THE UNIVERSITY *of* EDINBURGH

Development of Novel Metal-Catalysed Methods for the Transformation of Ynamides

Thesis Submitted in Accordance with the Requirements of The University of Edinburgh for the Degree of Doctor of Philosophy

By

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Declaration

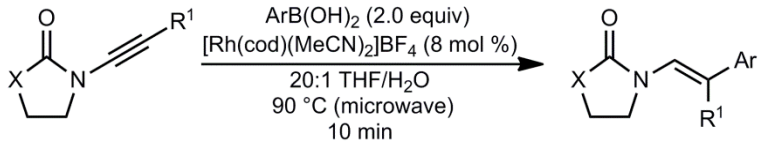
I hereby declare that, except where specific reference is made to other sources, the work contained within this thesis is the original work of my own research since the registration of the PhD degree in September 2009, and any collaboration is clearly indicated. This thesis has been composed by myself and has not been submitted, in whole or part, for any other degree, diploma or other qualification.

Donna L. Smith

Abstract

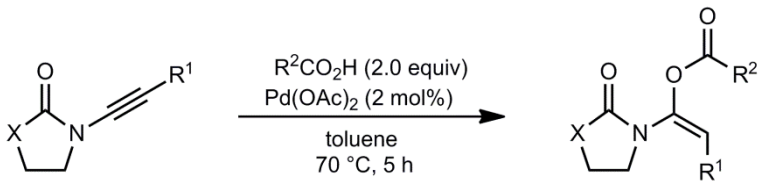
I. Rhodium-Catalysed Carbometalation of Ynamides using Organoboron Reagents

As an expansion of existing procedures for the carbometalation of ynamides, it was discovered that $[Rh(cod)(MeCN)_2]BF_4$ successfully promotes the carbometalation of ynamides with organoboron reagents. A variety of organoboron reagents were found to be suitable for this reaction, but mostly the use of arylboronic acids was explored. The developed methodology provides β,β-disubstituted enamide products in a regio- and stereocontrolled manner.



II. Palladium-Catalysed Hydroacyloxylation of Ynamides

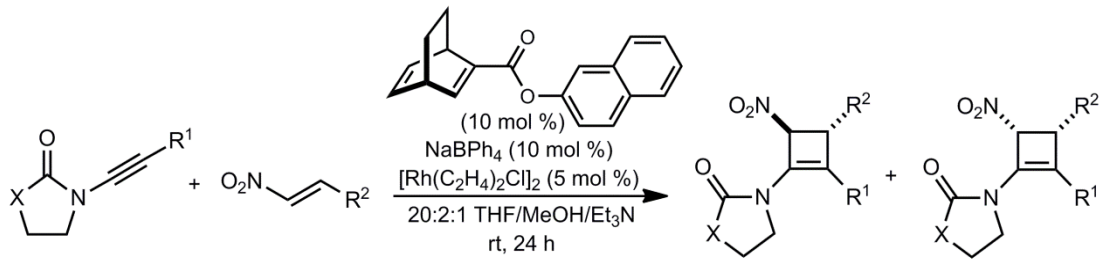
In the presence of palladium(II) acetate, ynamides successfully underwent a hydroacyloxylation reaction with a variety of carboxylic acids. This carboxylic acid addition occurred highly regio- and stereoselectively to provide α-acyloxyenamides. Applications of the α-acyloxyenamide products were also investigated.



III. Rhodium-Catalysed [2+2] Cycloaddition of Ynamides with Nitroalkenes

A novel rhodium catalyst system has been developed in order to promote the [2+2] cycloaddition reaction between ynamides and nitroalkenes. The reaction provides cyclobutenamide products and was diastereoselective in favour of the *trans*

cyclobutenamide. Both the ynamide scope and the nitroalkene scope of the reaction have been explored.



Contents

Acknowledgements

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Thank you to everyone in the Lam group past and present for making my time at Edinburgh very enjoyable. The group is now far too big to mention everyone individually, but all the lunchtime and coffee break chats always brightened up my day. You have been a great bunch to work and socialise with. Thanks especially to Benoit for showing me the ropes of the lab when I first started and sharing his tips on ynamide chemistry. Thank you to Graham and Sam for listening to all my comments, complaints and questions, and joining me on all the nights out. Thank you to Dan and Alan for providing advice during my thesis writing (your input definitely helped), and to Martin for some proof reading. Good luck with the rest of your research everyone.

Thank you to my family, for always supporting me and for putting up with all the time I have spent talking about and working on this thesis.

Abbreviations

Ac	acetyl
acac	acetylacetonate
AIBN	azobisisobutyronitrile
AD	asymmetric dihydroxylation
aq	aqueous
Ar	aryl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthalene
bipy	2,2'-bipyridyl
Bn	benzyl
Boc	*t*-butyloxycarbonyl
box	bisoxazoline
Bu	butyl
Bz	benzoyl
cat.	catalyst
Cbz	carboxybenzyl
cod	1,5-cyclooctadiene
conv	conversion
Cp*	1,2,3,4,5-pentamethylcyclopentadienyl
CPBA	chloroperbenzoic acid
Cy	cyclohexyl
d	doublet
dba	dibenzylideneacetone
DIBAL	di-*iso*-butylaluminium

DMAP	4-(dimethylamino)pyridine
DME	dimethoxyethane
DMEDA	dimethylethylenediamine
DMF	*N*,*N*-dimethylformamide
DMM	di(propylene glycol) dimethyl ether
dppb	1,4-bis(diphenylphosphino)butane
dr	diastereomeric ratio
E	electrophile
ee	enantiomeric excess
equiv	equivalents
Et	ethyl
EWG	electron-withdrawing group
Fur	furanyl
g	gram(s)
h	hour(s)
Hex	hexyl
HMDS	hexamethyldisilazane
i	iso
IMes	1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene
IR	infrared spectroscopy
L	ligand
LA	Lewis acid
m	multiplet
m	*meta*
M	molar; metal; Markovnikov

Mbs	4-methoxybenzenesulfonyl
Me	methyl
Mes	mesitylene
min	minute(s)
MS	molecular sieves
n.d.	not determined
NHC	*N*-heterocyclic carbene
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance spectroscopy
NOESY	nuclear Overhauser effect spectroscopy
Nu	nucleophile
o	*ortho*
Oct	octyl
o/n	overnight
Ox	2-oxazolidinone
p	*para*
Ph	phenyl
pin	pinacol
PNBSA	*p*-nitrobenzylsulfonic acid
Pr	propyl
q	quartet
R	alkyl/aryl group
rac	racemic
rr	regioisomeric ratio
rt	room temperature

s	singlet
t	triplet
t	tertiary
TBS	*t*-butyldimethylsilyl
temp	temperature
Tf	trifluoromethanesulfonate
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
tol	*p*-tolyl
Ts	tosyl
UV	ultraviolet
μW	microwave

1. Introduction

1.1 An Introduction to Ynamides

An ynamide is a compound that contains a nitrogen atom with both a carbon-carbon triple bond and an electron-withdrawing group directly attached.[1] This electron-withdrawing group is most often a carbonyl or a sulfonyl group. Some typical ynamide structures, and the associated ynamide subclass name, are shown in Figure **1.1**.

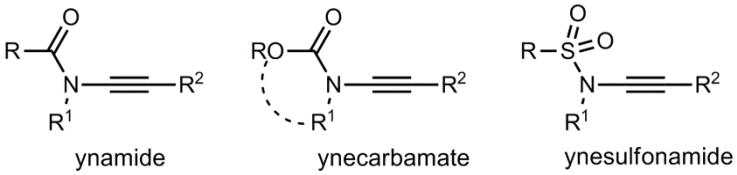
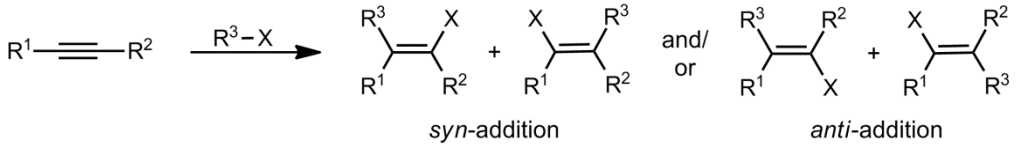


Figure 1.1

Alkynes are known to be extremely useful building blocks in organic synthesis; however, reactions involving intermolecular addition to alkynes (such as hydroarylation or hydroacyloxylation, discussed in Chapters 2 and 3 respectively) can often produce a mixture of possible product isomers (Scheme **1.1**).[2]



Scheme 1.1

The placement of a heteroatom at one end of the alkyne triple bond would help to resolve the issue of regioselectivity during addition. For example, the presence of the nitrogen atom within an ynamide polarises the triple bond, hence differentiating the reactivity at each end of the triple bond (Figure **1.2**). Thus, with ynamides both nucleophiles and electrophiles usually add to a specific site on the alkyne, in a

regioselective manner. The electron-withdrawing group of the ynamide can also influence reactivity by providing a handle, such as a carbonyl group, to which a metal can bind during a metal-catalysed reaction. This binding can dictate the regioselectivity of addition to the triple bond.

Figure 1.2

Ynamines, the predecessors to ynamides, can also react regioselectively due to polarisation of the triple bond. However, ynamines are hydrolytically unstable and thus difficult to handle and prepare. With ynamides, the presence of the electron-withdrawing group reduces the reactivity in comparison to ynamines, but consequently also makes the compounds much more stable and easier to handle. Ynamides can be purified by chromatography on silica gel and stored in the freezer for long periods of time.

Ynamides are very useful compounds as they provide a means for inclusion of nitrogen functionality into a target compound and they undergo a wide variety of transformations (Figure **1.3**). These transformations include additions to the triple bond, transition metal catalysed reactions, electrophilic reactions, alkyne reductions, cycloadditions, ring-closing metathesis and radical processes.

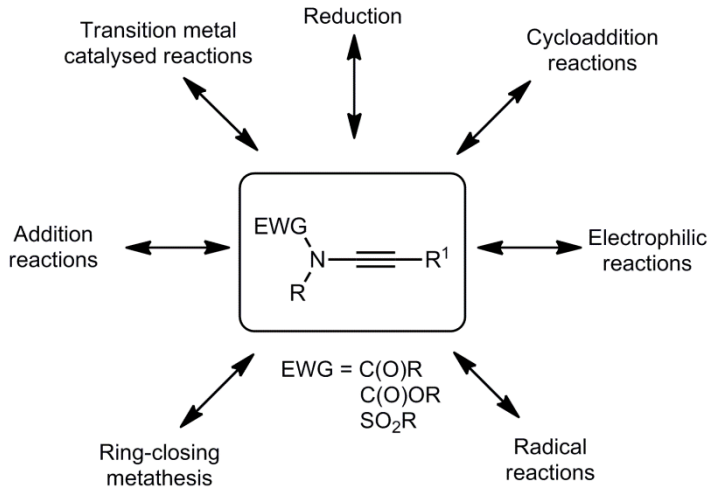
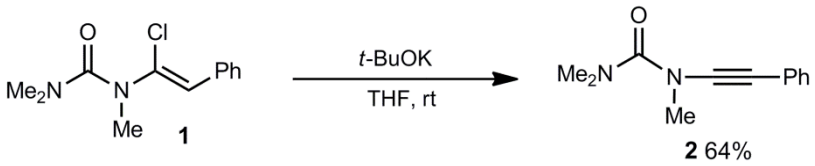


Figure 1.3

Although ynamides have been shown to participate in a wide variety of reactions (Figure **1.3**), many of these areas remain limited in their substrate scope and much potential remains for new ynamide reactions to be developed. Ynamides can provide a route to heterocycles,[3] natural products,[4] enamides,[5] and other novel compounds, but are underutilised. Thus, studying these very useful ynamide compounds and developing new reactions utilising them is definitely a worthwhile endeavour.

1.2 The Synthesis of Ynamides

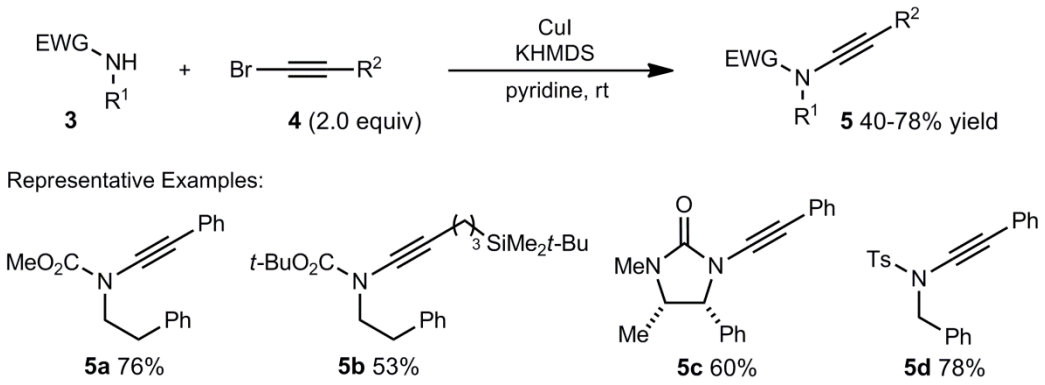
The first reported synthesis of an ynamide was by Veihe and co-workers in 1972.[6] The synthesis involved many steps culminating in elimination of HCl from urea-substituted chloroalkene **1** (Scheme **1.2**).



Scheme 1.2

In recent years, the synthesis of ynamides has become much more practical and concise, most commonly being accomplished by copper-catalysed coupling

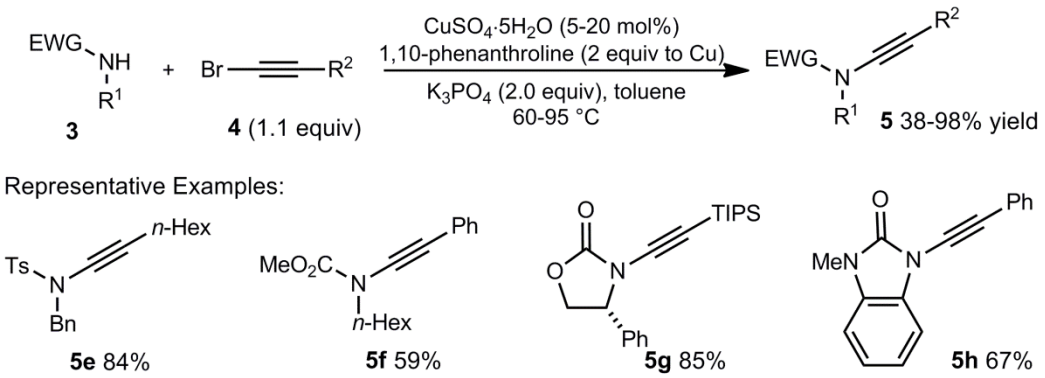
reactions. A number of groups have produced their own version of this copper mediated reaction. In 2003, Dunetz and Danheiser reported a synthesis of ynamides that used stoichiometric copper for the coupling of bromoalkynes with an appropriate nitrogen-containing compound (Scheme **1.3**).[7]



Scheme 1.3

This process operates at room temperature, with the isolated yields of the ynamides being moderate to good (**5a**-**d**). Mostly, carbamates were explored as the nitrogen component and phenyl-substituted alkynes appeared to provide the better yields (**5a**, **5d**). This procedure was one of the first practical and concise methods of ynamide synthesis, but unfortunately only a small range of ynamides was demonstrated. The base used is moisture sensitive and large quantities of pyridine are required, so scope remains for improved protocols for the synthesis of ynamides to be developed.

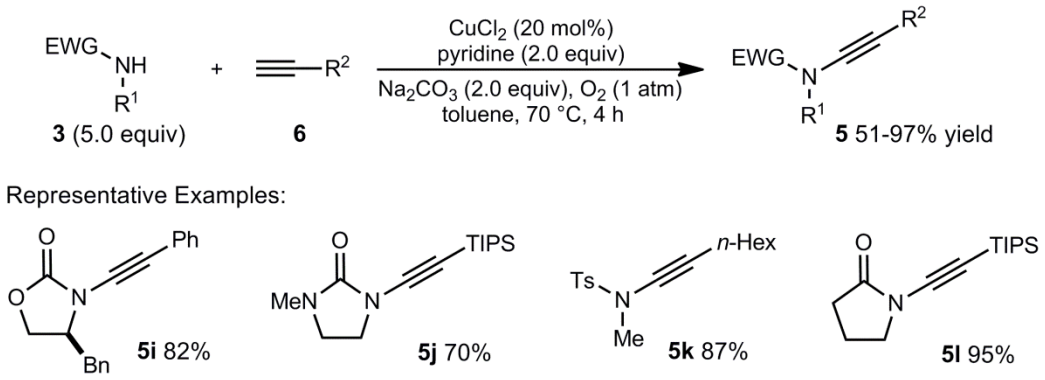
Hsung and co-workers improved on the copper-mediated coupling reaction by developing a catalytic procedure that was suitable for producing a wide range of ynamides and utilised an easier-to-handle inorganic base, K_3PO_4 (Scheme **1.4**).[8]



Scheme 1.4

The yields still varied from moderate to excellent, but generally improved yields on that reported by Dunetz and Danheiser[7] were achieved. The exact mechanism of the Hsung procedure is unascertained.

A direct coupling method where no prior halogenation of the alkyne is required was developed by Stahl and co-workers in 2008 (Scheme **1.5**).[9] This direct coupling was achieved by utilising aerobic re-oxidation of the copper catalyst.

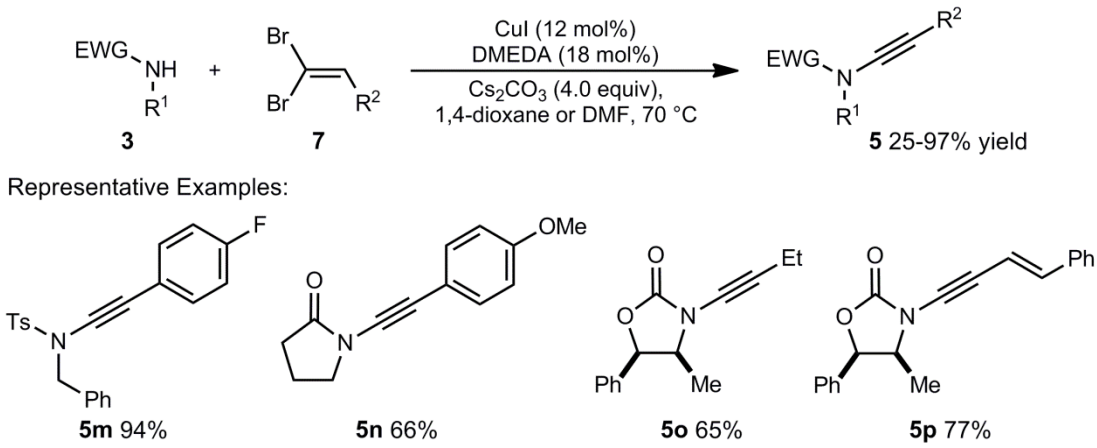


Scheme 1.5

The synthesis of a large number of ynamides was reported, mostly in high yield (**5i-l**). However, some substrate limitations were apparent as acyclic carbamates were unreactive and reaction of pyrrolidinone was only successful with one of the alkynes tried (**5l**). In general, the reaction proceeds rapidly, but slow addition of the alkyne over the four hours and a large excess of the nitrogen component were required to

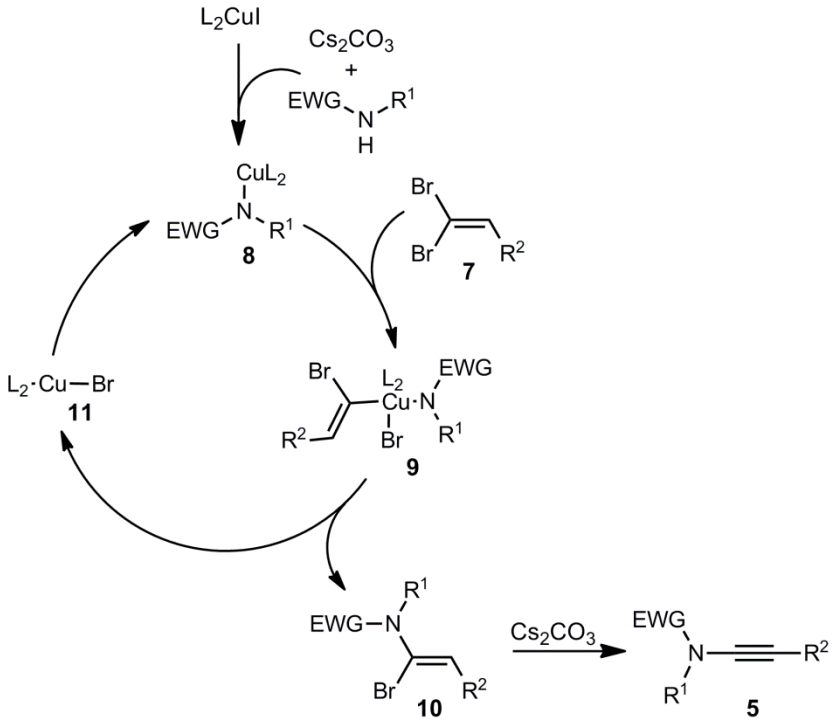
prevent alkyne homocoupling. This direct coupling procedure is advantageous as commercially available alkynes can be immediately utilised.

A more recent procedure by Evano and co-workers[10] utilised dibromoalkenes, instead of alkyne-based coupling partners, which is useful when the corresponding alkyne is expensive or unavailable. Dibromoalkenes (**7**) are synthesised from an aldehyde and as aromatic aldehydes are more commercially available than aromatic alkynes, a wider variety of aryl substituents were incorporated into the ynamides reported in this publication (**5m**, **5n**).



Scheme 1.6

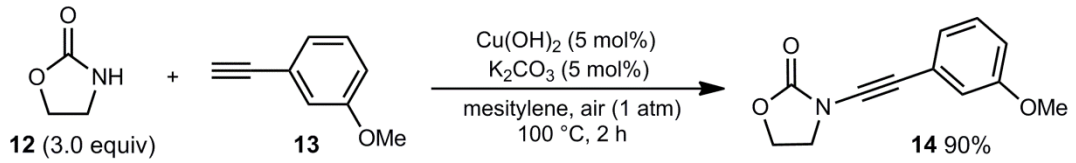
The yields from this procedure were again variable, but a wide variety of ynamides could be prepared, in at least 60% yield in most cases (**5m**-**p**). Some pyrrolidinone-based ynamides, such as **5n**, were produced in surprisingly high yield compared to the results reported by Stahl and co-workers.[9] The reported mechanism for the reaction is shown below (Scheme **1.7**).



Scheme 1.7 – Drawn as specified in the relevant publication[10]

The mechanism occurs by coordination of the nitrogen coupling partner to copper to give **8**, and then oxidative addition of the C-Br bond of the dibromoalkene that is *trans* to the R^2 group to give **9**. Reductive elimination of **9** then produces intermediate **10**, which undergoes base-promoted HBr elimination to produce the ynamide. It is known that the *trans* C-Br bond is the most reactive of the dibromoalkene bonds to oxidative addition,[11] and further evidence for this mechanism was obtained as intermediate **10** could be isolated and transformed into an ynamide by treatment with cesium carbonate.

Mizuno and co-workers recently published a method for the synthesis of ynamides where terminal alkynes are used with simply air as the oxidant.[12] This direct coupling method seems to be an improvement on Stahl's method[9] as access to oxygen gas is not required. A number of slight variations in the conditions, mostly the inorganic base used and the catalytic loadings, are reported. A representative example reaction is shown in Scheme **1.8**.



Scheme 1.8

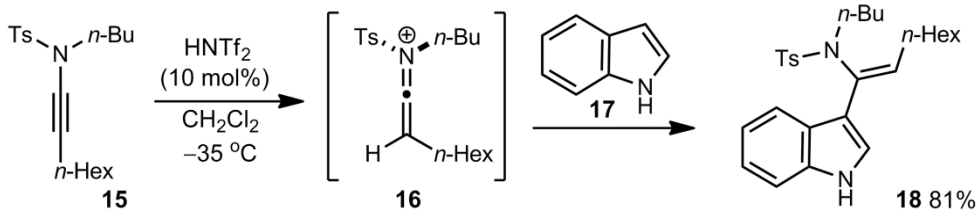
These coupling reactions proceed very rapidly, in comparison to most methods for the synthesis of ynamides, and the yields reported for oxazolidinone-based ynamides are high (**14**). However, only a very limited reaction scope is demonstrated, with nearly all examples reported being of oxazolidinone-based ynamides and the one reported synthesis of an ynesulfonamide, using Cu_2O, occurring in a moderate yield. Overall, this direct alkyne coupling procedure would be advantageous when synthesising oxazolidinone-based ynamides, but its applicability for large-scale synthesis or other ynamide subclasses remains to be explored.

In conclusion, a number of copper-mediated coupling methods have been discussed for the synthesis of ynamides. These procedures all have their own advantages and the most appropriate coupling method for the available starting materials and reagents should be used.

1.3 The Reactivity of Ynamides

A number of reviews on the chemistry of ynamides have been published,[1] so only a brief overview of the many reactions involving ynamides will be discussed here. The following examples are designed to highlight the main reaction classes that ynamides can participate in (see Figure **1.3**). In addition, a number of [2+2] cycloaddition reactions involving ynamides will be discussed in Chapter **4.1**.

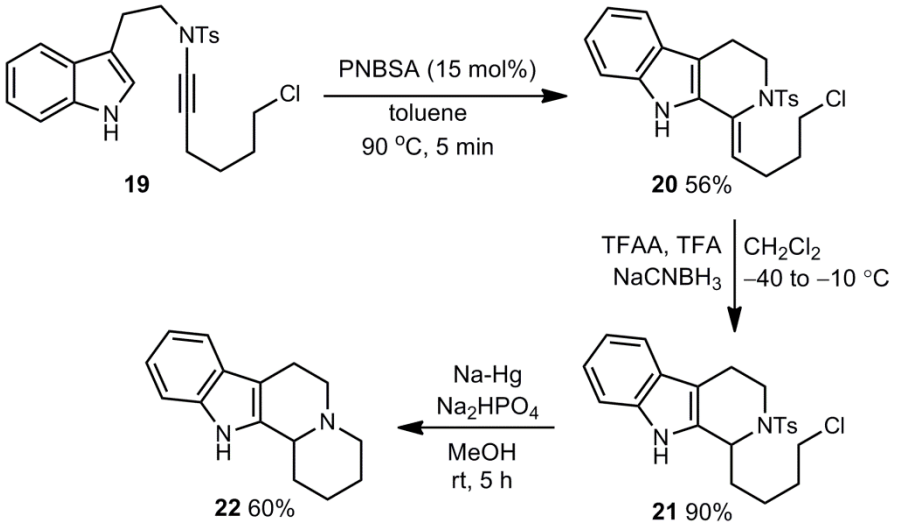
An example of ynamides reacting as electrophiles, through a keteniminium intermediate, has been provided by Zhang.[13] Here, regioselective hydroarylation of ynamides was accomplished, using Brønsted acid catalysis, to provide *Z*-vinylindoles (**18**; Scheme **1.9**).



Scheme 1.9

The ynamide is protonated by the triflimide catalyst, and then keteniminium intermediate **16** reacts with an indole. Various ynesulfonamides and an ynecarbamate reacted in high yield and selectivity, but the ynamide scope explored was still limited. This hydroarylation protocol can be extended to include the addition of furans and pyrroles to the ynamide.[14] Zhang's publication illustrates the reactivity of ynamides and provides synthetically useful, pharmaceutically sought after *Z*-vinylindole products.

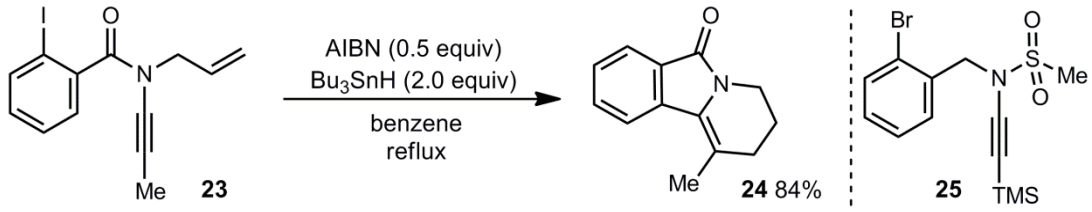
Hsung and co-workers utilised hydroarylation chemistry for the synthesis of a natural product (Scheme **1.10**).[4a] An indole-tethered ynamide (**19**) underwent intramolecular arylation, using *p*-nitrobenzene sulfonic acid as the Brønsted catalyst, to produce intermediate **20**.



Scheme 1.10

Reduction of the alkene present in intermediate **20** was accomplished using acidic sodium cyanoborohydride conditions (**21**), then reductive de-tosylation followed by spontaneous cyclisation both occurred under Smith's protocol using sodium amalgam.[15] The formation of the natural product 10-desbromoarborescidine A (**22**) resulted. This publication provides a good illustration of how ynamides can be employed in total synthesis.

The first publication on the use of ynamides in radical reactions was reported by Malacria and co-workers in 2003.[16] The reported reactions utilised ynamides to generate elaborate nitrogen-containing polycyclic compounds in one step (Scheme **1.11**).

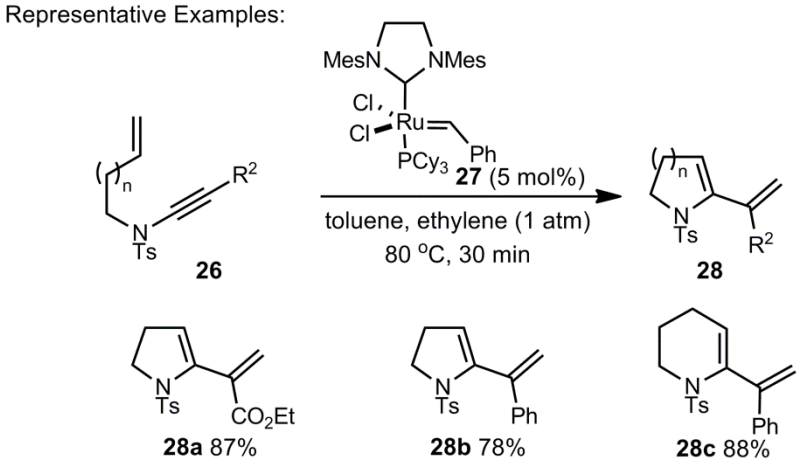


Scheme 1.11

A number of substituted amides, for example **23**, underwent radical cyclisation successfully, but simpler ynesulfonamides (such as **25**) did not.[17] The cyclisation reaction proceeds through cleavage of the carbon-halogen bond by a tin radical, generating an aryl radical that attacks the ynamide triple bond. The resulting vinylic radical then reacts with an alkenyl or aryl group tethered to the nitrogen atom, generating a polycylic product such as **24**.[18]

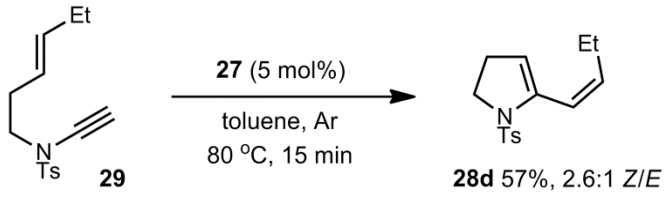
This publication demonstrates an excellent first application of ynamides in radical chemistry, in terms of the useful polycyclic structures obtained; however, the use of tin compounds is unfavourable in many situations, due to their toxicity. The development of similar ynamide radical reactions with alternative reagents would be desirable, perhaps using tris(trimethylsilyl)silane[19] or diethylphosphine oxide[20] as alternatives to tributyltin hydride.

A pioneering publication on ring-closing metathesis of ynamides was published by Sato and co-workers in 2006.[21] The second-generation Grubbs' ruthenium catalyst **27** was used to obtain the resulting dienamide products (Scheme **1.12**).



Scheme 1.12

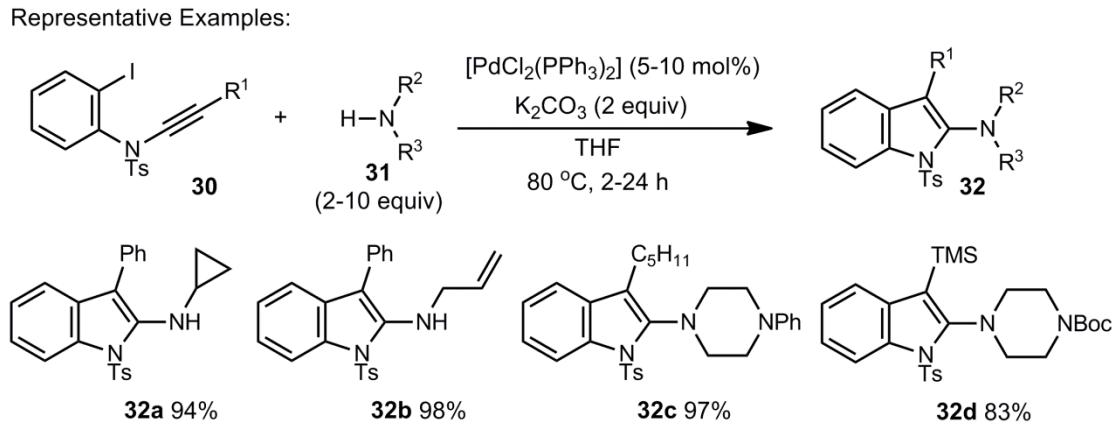
Some ynamides resulted in a very high yield after ring-closing metathesis (**28a**, **28c**), but examples containing an internal alkene resulted in a lower yield and a poor *E*/*Z* ratio (Scheme **1.13**). For most substrates, a higher yield resulted when the reaction was conducted under an ethylene atmosphere. However, for ynamide substrates containing an internal alkene (**29**) an argon atmosphere was required.



Scheme 1.13

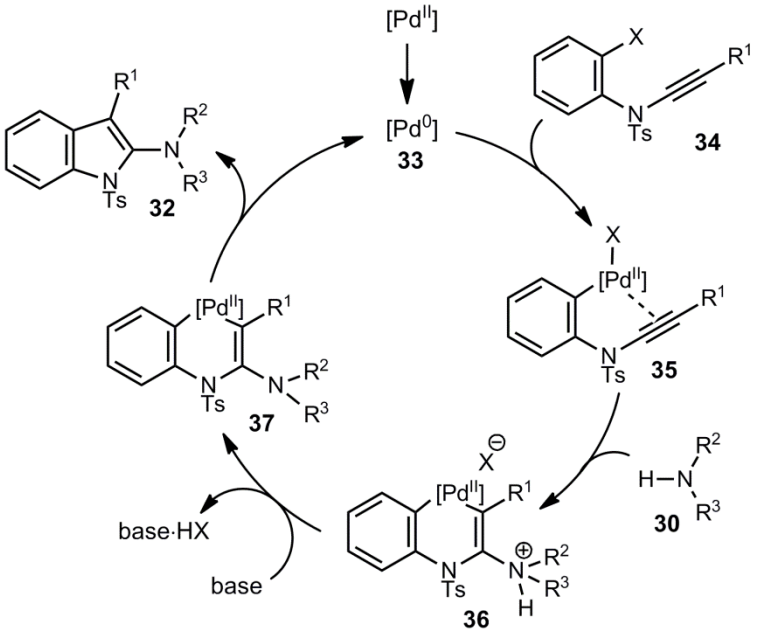
Ring-closing metathesis is often used as a critical step in natural product synthesis,[22] so the inclusion of ynamides within the scope of ring-closing metathesis is advantageous and has potential applications in the synthesis of enamide-containing natural products (see Chapter 2.1).

The majority of ynamide reactions involve metal catalysis. One mode of ynamide activation by a metal catalyst, π-Lewis acid activation, is clearly shown in Witulski and co-workers' procedure of 2-aminoindole synthesis.[3a] Here, palladium catalysis is used and addition of an amine to the activated ynamide occurs, in a regioselective manner, to provide an indole (**32**).



Scheme 1.14

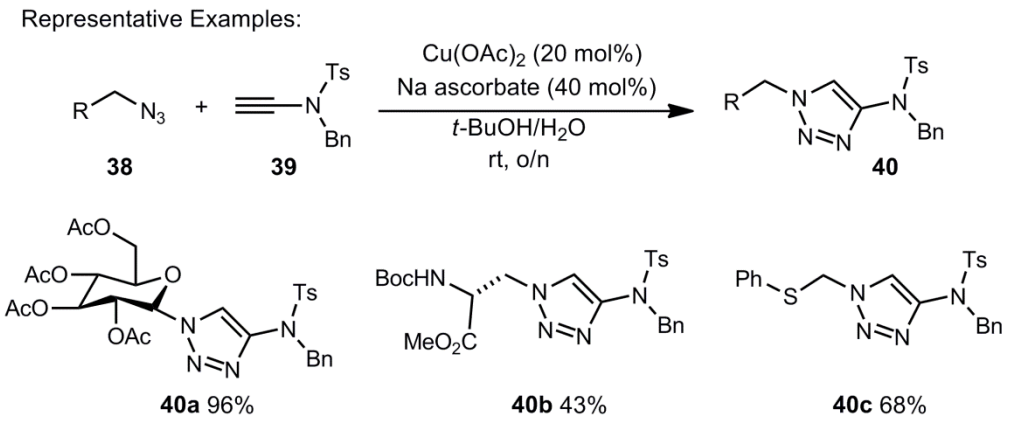
Very high yields were achieved with a number of tosyl-based ynamides (**30**) and a wide range of primary or secondary amines (**32a-d**). In this procedure, the use of ynamides was advantageous as the resulting tosylated products (**32**) are stated to be more stable towards hydrolysis than the parent 2-aminoindoles. The reported mechanism for the reaction is shown in Scheme **1.15**. Firstly, *in situ* palladium(0) formation is believed to occur. Then oxidative addition of the aryl-halide bond of **34** takes place and the ynamide is activated by π-Lewis acid coordination to the resulting palladium(II) centre (**35**). Addition of an external amine to the activated ynamide then occurs in a regioselective manner, to give **36**. Finally, reductive elimination produces the 2-aminoindole product (**32**).



Scheme 1.15 – Drawn as specified in the relevant publication[3a]

Indole compounds are prevalent in medicinal chemistry and natural alkaloids; hence new methods for their synthesis are always advantageous. This publication has produced a novel, diversity orientated approach, whilst highlighting the importance of ynamide chemistry.

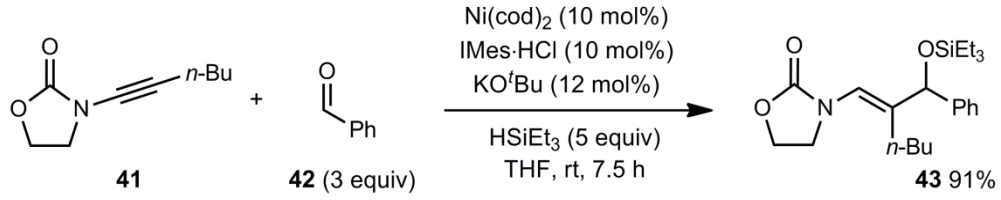
An example of an ynamide participating in a cycloaddition reaction is provided by Ijsselstijn and Cintrat's publication reporting the first "click" reaction of ynamides.[23] Here, the developed [3+2] cycloaddition reaction between ynesulfonamides (**39**) and various alkyl azides (**38**) generated amino-substituted triazoles (**40**) in varying yields. A catalytic system consisting of a copper(II) source that is reduced *in situ* to copper(I) by sodium ascorbate was found to successfully promote the desired reaction.



Scheme 1.16

An excellent yield was obtained from utilising an acetate-protected sugar azide (**40a**), but the other yields obtained were largely more moderate (**40b**). The resulting triazoles possessed a wide variety of interesting substituents, as potentially biologically active compounds were targeted by the authors. Only terminal ynamides were explored by the authors, due to the nature of this click reaction, which normally proceeds through a copper acetylide intermediate.

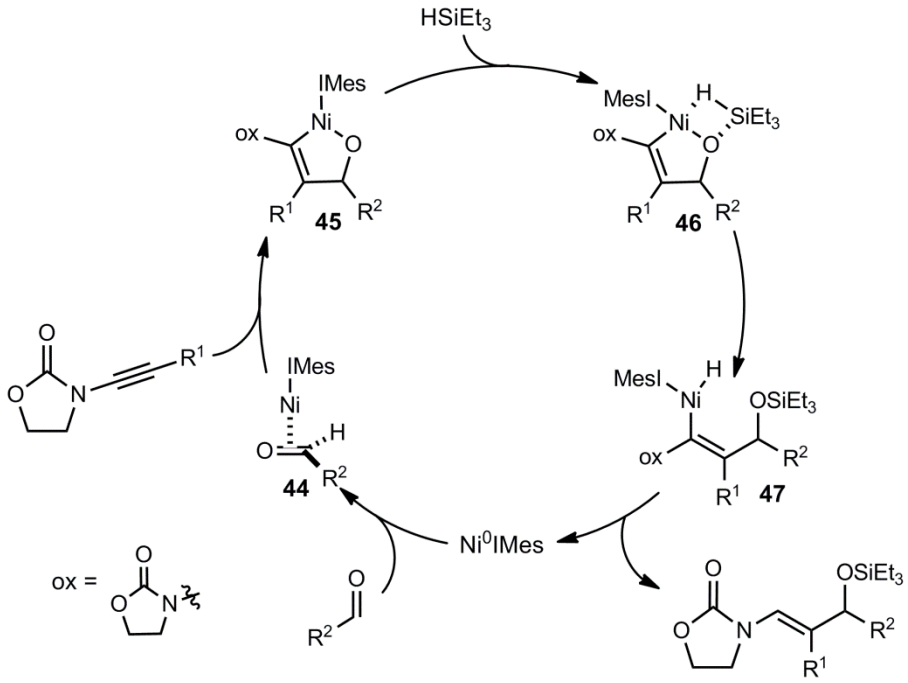
An example of a metal-catalysed nucleophilic reaction of ynamides has been reported by Sato and co-workers.[24] In this nickel-NHC-catalysed multi-component reaction, ynamides add to an aldehyde and the final products are γ-silyloxyenamides (Scheme **1.17**).



Scheme 1.17

Slow addition of the ynamide to the reaction mixture, over seven hours, was found to suppress byproduct formation and produce desired product **43** as a single regio- and stereoisomer. Exploration of the substrate scope using various aldehydes or other oxazolidinone-based ynamides, provided a variety of γ-silyloxyenamides in moderate

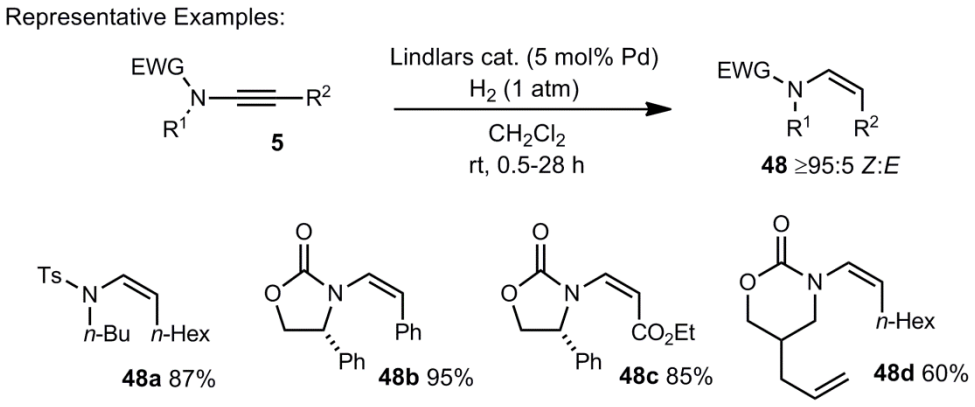
to high yields. The proposed mechanism (Scheme **1.18**) involves aldehyde activation through coordination to the nickel (**44**). The ynamide then adds to this activated aldehyde and metallocycle **45** is formed. Subsequently, involvement of the silane reagent is believed to occur, cleaving the metallocycle (**47**). Reductive elimination then releases the desired product.



Scheme 1.18 - Drawn as specified in the relevant publication[24]

This publication provides a route to potentially useful, functionalised enamide products and demonstrates the reaction of an ynamide through its more nucleophilic β-carbon.

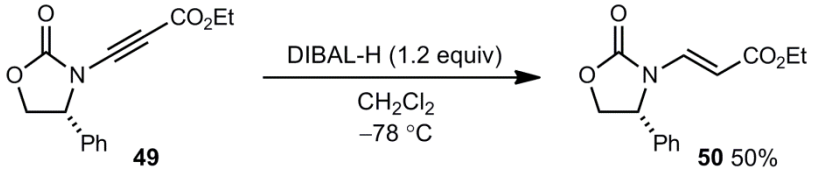
Stereoselective reduction of the ynamide triple bond was demonstrated by Hsung and co-workers in a 2006 publication.[25] Lindlar's catalyst was used to accomplish the stereoselective hydrogenation of a variety of ynamides to produce *Z*-enamides (Scheme **1.19**). This method is beneficial as highly stereoselective synthesis of *Z*-enamides, typically attempted from non-ynamide starting materials, was previously difficult to accomplish.



Scheme 1.19

The reactivity of the ynamides and hence the reaction time varied, but a good yield of the corresponding *Z*-enamide was achieved in all cases. For example **48d**, the presence of alkene functionality was well tolerated under the reaction conditions.

One example of reduction to an *E*-enamide was reported (Scheme **1.20**). This reduction was accomplished using diisobutylaluminium hydride and involved alkynoate-substituted ynamide **49**.



Scheme 1.20

In conclusion, the above section has highlighted that ynamides have a wide variety of applications and can take part in a diverse range of transformations. These transformations result in sought after or synthetically useful compounds, such as heterocycles, natural products and functionalised enamides.

Using the reactions described in this section, along with a more general survey of the literature involving reactions of ynamides, some comparisons of ynamide reactivity with the reactivity of more common carbon-substituted alkynes can be attempted. Firstly, in reactions where two new bonds are formed to each end of the alkyne,

ynamides have a greater tendency to react with high regioselectivity than other internal carbon-substituted alkynes. Some evidence for this statement is that a hydroarylation of ynamides (Scheme **1.9**) occurred readily and regioselectively using simple acid catalysis, whereas, while an equivalent Friedel-Crafts-type reaction has been reported for carbon-substituted internal alkynes,[26] regio- and stereoselectivity were an issue. Secondly, a number of reactions occur more feasibly with ynamides than carbon-substituted alkynes. For example, the ynamide reactions involving a radical cyclisation cascade, amination of the triple bond followed by carbocyclisation or nucleophilic addition to an aldehyde (Schemes **1.11**, **1.14** and **1.17** respectively) are thought not to have been reported in an equivalent manner with internal carbon-substituted alkynes. These reactions likely occur successfully and regioselectively with ynamides due to the electronic nature of the nitrogen-substituted alkyne. Finally, some reported reactions of ynamides appear to be an extension of reactions developed for carbon-substituted alkynes, but with the added benefit of the inclusion of nitrogen functionality. The described ring-closing metathesis, [3+2] cycloaddition and hydrogenation reactions of ynamides (Schemes **1.12**, **1.16** and **1.19** respectively) are known to occur with carbon-substituted alkynes under similar conditions.[27-29]

1.4 Conclusions

Ynamides are very useful compounds as they can successfully take part in a variety of transformations. Ynamides can be used in metal-catalysed or radical reactions to produce synthetically useful products, or even be involved in the total synthesis of natural products. Most reactions of ynamides have only been developed within the last decade and there is still potential for new reactions to be discovered.

Ynamides have an ability to react with enhanced regioselectively compared to internal carbon-substituted alkynes, due to the electronically-biased nature of the ynamide triple bond and the added ability of the electron-withdrawing group to coordinate to metal centres; however, the full extent of this ability remains to be explored. Also, the polarisation and electron rich nature of the ynamide triple bond

can cause some reactions to occur more feasibly and readily with ynamides than with simpler carbon-substituted alkynes.

The available protocols for the synthesis of ynamides have improved within the last decade, becoming higher yielding, more concise, atom-economic and environmentally acceptable. The majority of ynamides are now synthesised by copper-catalysed coupling procedures. The improvement in the ease of preparation of ynamides has largely inspired the occurrence of novel reaction development using ynamide substrates.

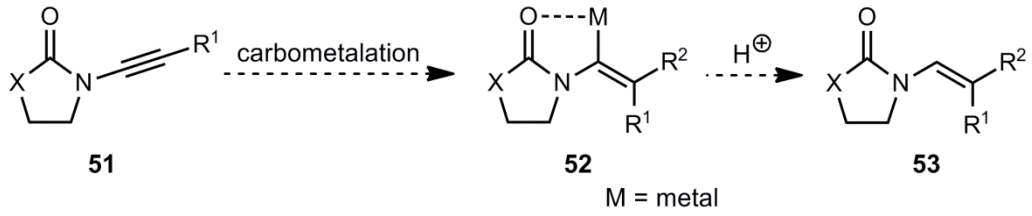
1.5 Overall Aims for Forthcoming Chapters

Ynamides have been shown in the literature to undergo a wide variety of transformations and provide synthetically useful products;[1] however, much potential remains for new ynamide reactions to be developed. As the Lam group focuses on metal-catalysed reaction methodology, the ability of the ynamide to coordinate to a metal centre, either through the alkyne or electron withdrawing group components, and the new reactions that this can uncover was of interest. The aim of this research is to explore the reactivity of ynamides in transition metal-catalysed reactions and to develop novel reaction methodology utilising ynamides. In addition, novel compounds will be synthesised that had not previously been attainable.

This work will help to expand on the available literature regarding the synthetic utility of ynamides, and will build on previous methodology developed within the Lam group, namely, a procedure for rhodium-catalysed carbometalation of ynamides using organozinc reagents. As this procedure provides multisubstituted enamides, the synthesis of further enamide structures or derivatives, starting from ynamides, will be explored.

2. Rhodium-Catalysed Carbometalation of Ynamides with Organoboron Reagents

Enamides are useful compounds in synthesis[30-32] but enamide formation is nontrivial. Synthesis of enamides in a stereo- and regiocontrolled fashion has been a problem in the past (see Chapter 2.2). Development of an efficient route to β,β-disubstituted enamides **53** from simple precursors would be advantageous. This synthesis has previously been achieved through carbometalation of ynamides (Scheme **2.1**).[5b,33] Carbometalation normally occurs in a *syn* fashion, which would control the stereoselectivity of the reaction. It was also anticipated, from literature precedent,[5b,33] that the metal used would bind to the oxygen within the ynamide carbonyl group (**52**), resulting in a highly regioselective reaction. These combined mechanistic features would generate a single isomeric enamide product.



Scheme 2.1

Previously published methods for the carbometalation of ynamides make use of highly reactive organometallic reagents,[5b,33] which require special handling conditions and have low functional group tolerance. In the past, the Lam group has used organozinc reagents along with rhodium catalysis.[33] The development of a method that does not require the highly reactive organozinc reagents is desirable. Boronic acids are known to transmetalate with various metal catalysts and have high stability and functional group tolerance.[34] Therefore, the use of organoboron reagents in the carbometalation of ynamides presents a potential solution.

In the following section, a newly developed rhodium-catalysed carbometalation of ynamides with organoboron reagents is described. This reaction provides an efficient route to β,β-disubstituted enamides.

2.1 Introduction

2.1.1 Introduction to Enamides

Enamides are useful compounds in organic synthesis; they have many potential applications and provide varied opportunities for the inclusion of nitrogen-based functionality.[30] All enamides have a nitrogen atom which is directly attached to both an electron-withdrawing group and an alkene (Figure **2.1**).

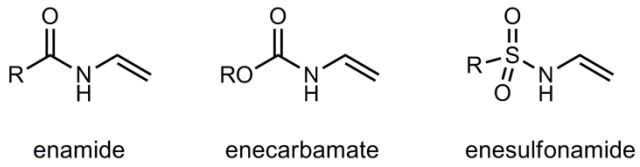


Figure 2.1

Enamines are known to be highly useful enolate equivalents, for example in organocatalysed Michael addition reactions[35] or the α-alkylation of ketones,[36] but enamines are susceptible to protonolysis and hydrolysis. Enamides possess the nucleophilic characteristics of an enamine, but the presence of the electron-withdrawing group reduces this reactivity and makes enamides much more stable than enamines. Also, enamides possess tuneable reactivity through variation of the electron-withdrawing group and are useful for a wider variety of transformations.[30]

Additionally, enamides are present in a number of natural products, making enamides a very worthwhile target for reaction development. These natural products include the cell cycle inhibitor terpeptin,[37,38] an indole-containing peptide, and the benzolactone phosphatase inhibitor oximidine III[39] (Figure **2.2**), both of which have *anti*-tumour activity.

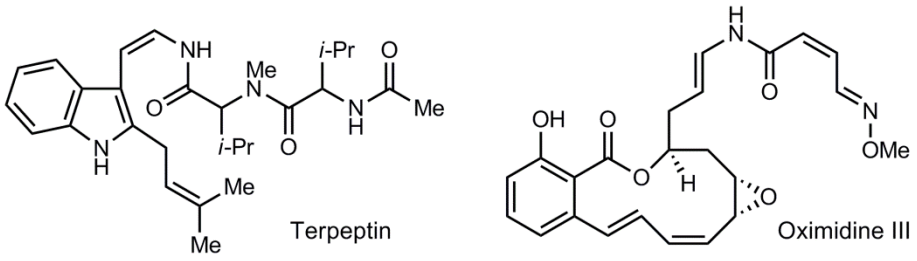
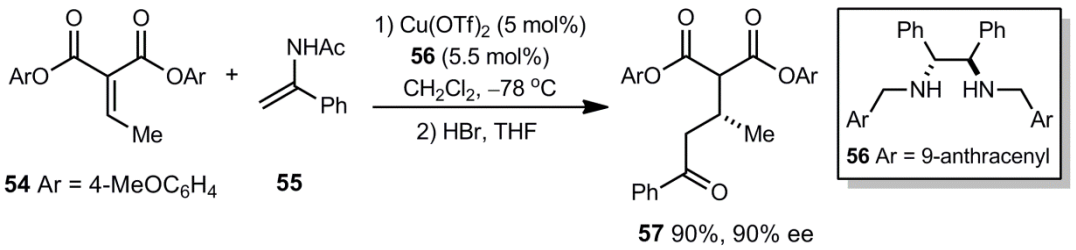


Figure 2.2

2.1.2 Reactions of Enamides

Detailed discussions of the reactions of enamides can be found in reviews by Carbery[30a] and Kobayashi.[30b] Only a small number of examples will be discussed here in order to highlight the synthetic utility of enamides.

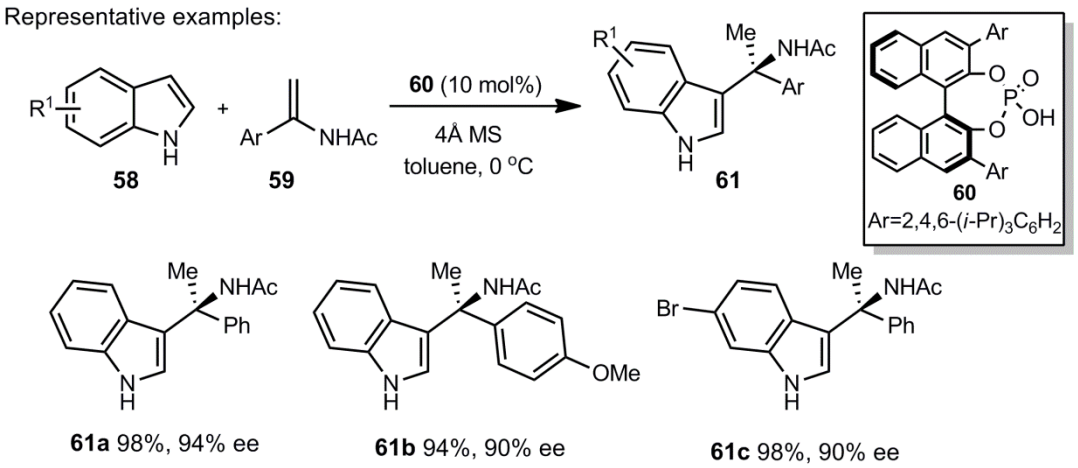
A demonstration of the ability of enamides to react as nucleophiles in Michael addition reactions was published by Kobayashi and co-workers in 2007.[31] Here, ethylidenemalonantes (such as **54**) were used as the Michael acceptor and Lewis acid catalysis with copper(II) and chiral diamine ligand **56** promoted the reaction. Then the intermediate iminium ion produced from Michael addition was hydrolysed with aqueous acid to provide enantioenriched 1,5-dicarbonyl compounds (**57**).



Scheme 2.2

Some very high yields and enantioselectivities were obtained (**57**), with a number of different α-substituents on the enamide being well tolerated. Substrate **54** was found to provide the highest yields of the Michael acceptors explored, and enecarbamates could also be employed. This publication has illustrated a very useful nucleophilic reaction of enamides, where 1,5-dicarbonyl compounds are produced enantioselectively.

Enamides can react as electrophiles through conversion to an iminium ion under acidic conditions. Zhou has utilised α-aryl enamides as masked electrophiles in an enantioselective Friedel-Crafts reaction.[32] Here, phosphoric acid-catalysed reaction of enamides with indoles generates quaternary stereocentre-containing products (**61**).



Scheme 2.3

In general, excellent yields and enantioselectivities were obtained (**61a-c**), with most aryl substituent variations on both the enamide and indole well-tolerated. A mechanistic insight was provided by the discovery that the NH groups on both the indole and enamide starting materials are crucial for the reaction to occur, as *N*-methylated substrates gave no desired product. It appeared likely that hydrogen bonding of these NH groups to the phosphoric acid catalyst was occurring. The proposed transition state is shown in Figure **2.3**.

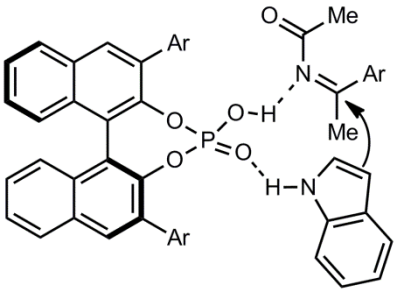


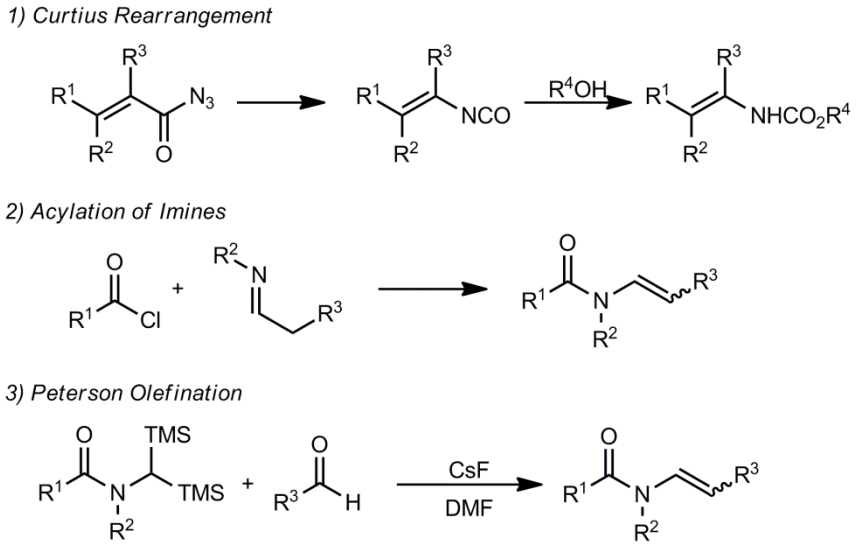
Figure 2.3

This reaction by Zhou is an interesting example of enamides as electrophiles, and generates nitrogen-bearing quaternary carbon centres that are very common in natural alkaloids.

In addition to the nucleophilic and electrophilic reactivity of enamides, other synthetically useful applications of enamides include asymmetric hydrogenation,[40] Diels-Alder reactions,[41] Heck reactions,[42] and participation in total synthesis.[43]

2.1.3 Synthesis of Enamides

Enamide derivatives are often the resulting products of reactions involving ynamides (Chapter **1.2**). However, a number of procedures also exist for the more direct synthesis of enamides from non-ynamide starting materials. Some more traditional syntheses of enamides (Scheme **2.4**) have included the Curtius rearrangement of α,β-unsaturated acyl azides followed by reaction with an alcohol,[44] the acylation of imines,[45] and the olefination of amides.[46]

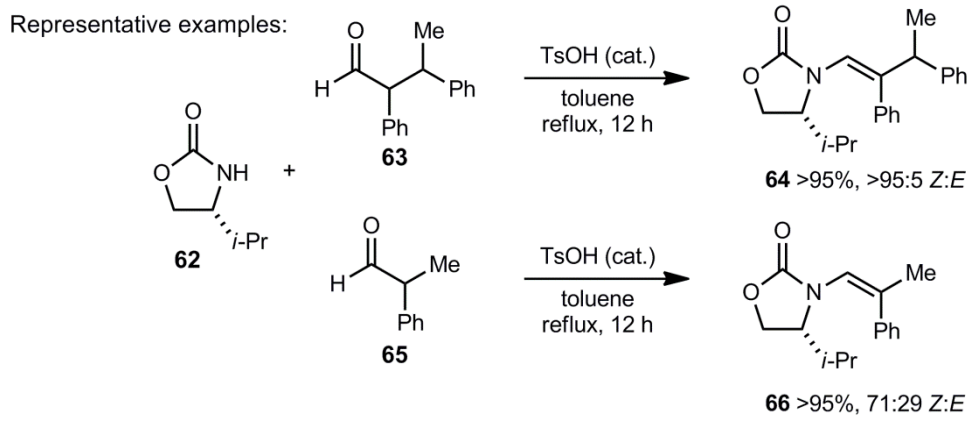


Scheme 2.4

These methods (Scheme **2.4**) were often low yielding and required harsh conditions, with low functional group tolerance. In addition, the starting materials typically

required numerous steps to synthesise and the resulting enamide products were often produced as a mixture of inseparable isomers.

A more concise approach to the synthesis of enamides was taken by Adam and co-workers, who described the formation of enamides through condensation of an amide with an aldehyde;[47] however, this method still suffers from some of the drawbacks mentioned above. The condensation reaction was catalysed by *p*-toluenesulfonic acid and used Dean-Stark apparatus (Scheme **2.5**). All of the reactions reported had a yield of greater than 95%, but there were issues with the stereoselectivity of the reactions.

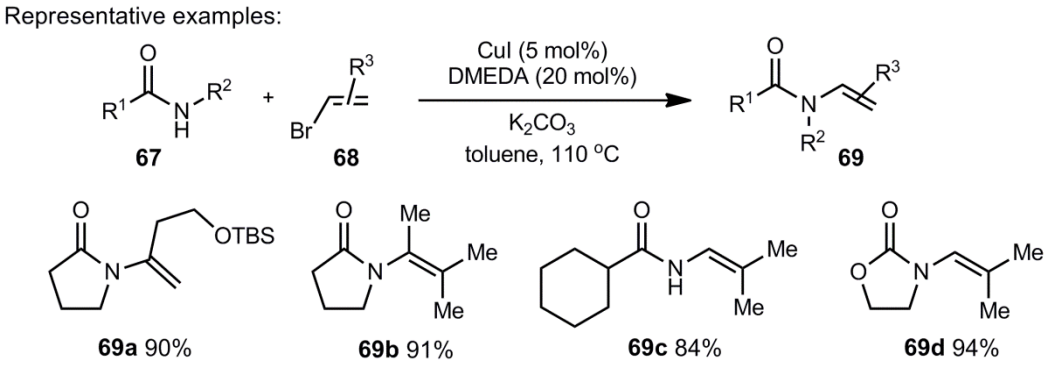


Scheme 2.5

The stereoselectivity was excellent in reactions using aldehyde **63** and different oxazolidinone substrates (for example **62**). However, when the aldehyde contained a smaller α-methyl group (**65**) in place of the bulkier α-group, selectivity was poor. This procedure for the synthesis of enamides would be useful in select cases, but it is limited to formation of β-substituted enamides. A more functional group tolerant method, with consistently high stereoselectivity is required.

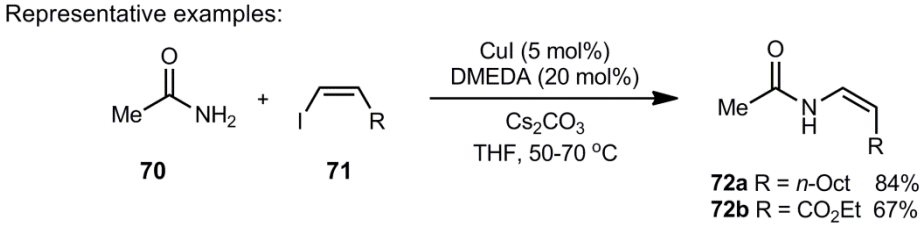
More recently, metal-catalysed coupling methods have been developed for the synthesis of enamides,[48,49] in order to produce a more stereoselective synthesis and remove the traditional need for harsh conditions. In this pursuit, Buchwald and co-workers carried out amidation of vinyl halides using copper catalysis (Scheme **2.6**).[50]

These reactions are believed to occur with retention of the alkene geometry (see **72a**, **72b**).



Scheme 2.6

With vinyl bromides (**68**), cyclic amides, acyclic primary amides and cyclic carbamates were all found to react in good yield (**69a-d**); however, acyclic secondary amides were not successful. Different substitution patterns on the vinyl bromide, and a silyl ether substituent (**69a**) were well tolerated. For reactions involving a vinyl iodide, the conditions differed (Scheme **2.7**). These reactions could be successfully carried out at lower temperatures (for example **72a**). The use of α,β-unsaturated ester derivatives was also found to be viable (**72b**), providing β-amino acid precursors.

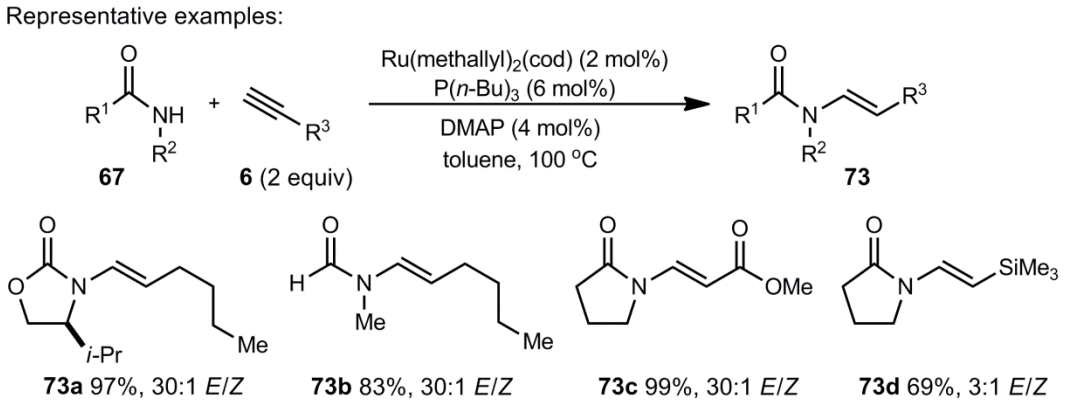


Scheme 2.7

Whilst this method by Buchwald and co-workers mostly provides high yields and uses milder conditions than traditional syntheses, only a limited range of alkenyl halides are commercially available and the synthesis of alkenyl halides, in the required geometry, is often very difficult. In general, metal-catalysed coupling methods are a vast improvement on previous synthesis routes to enamides, but there

are still difficulties in the preparation of coupling partners and some limitations with respect to the enamides that can be produced.

Hydroamidation of terminal alkynes can also be utilised for the synthesis of enamides.[51] This method is very atom-economic and does not rely on vinyl halide synthesis. In a publication by Gooβen and co-workers,[51b] stereoselective hydroamidation was efficiently achieved using ruthenium catalysis (Scheme **2.8**). Many iterations of the catalytic system were tried before simultaneous high yield and selectivity were obtained.



Scheme 2.8

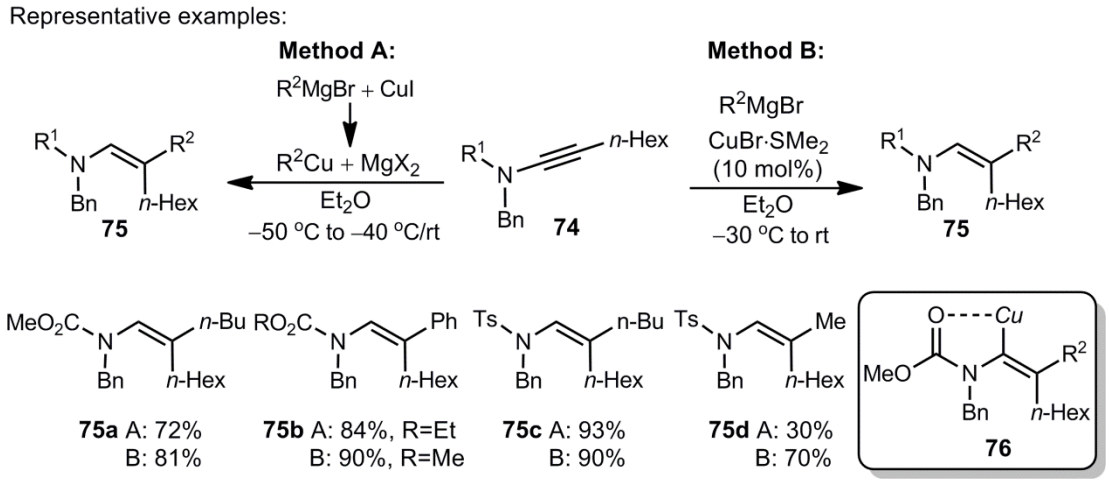
A range of nitrogen nucleophiles were successful in this reaction, including acyclic secondary amides (**73b**), and sensitive functional groups were well tolerated (**73b**, **73c**). Most products were isolated in an excellent isomeric ratio (**73a-c**); however, a small number of enamides were generated with poor selectivity (including **73d**). An alternative ligand system for the formation of *Z*-enamides was also disclosed, but only two results were communicated and the selectivity was subsequently improved by development of a related protocol.[52] Overall, Gooβen's method provides a large number of *E*-enamides in high yield and selectivity, but there is a distinct limitation of the hydroamidation route, in that only β-monosubstituted enamides were prepared.

Despite the recent advances for the successful preparation of enamides, there is still a requirement for further practical, flexible, and stereoselective approaches to the

synthesis of enamides to be developed. Efficient methods that use commercially available reagents and provide multi-substituted enamides would be highly desirable.

2.1.4 Carbometalation of Ynamides

The carbometalation of ynamides can provide a stereoselective route to β,β-disubstituted enamides; however, there are few literature examples of these reactions.[5b,33,53] The first publication on intermolecular carbometalation of ynamides was provided by Marek and co-workers in 2005.[5b] Regio- and stereoselective formation of β,β-disubstituted enamides was reported, using two slight variations in method. Firstly, carbocupration using organocopper reagents pre-prepared *in situ* from Grignard reagents, was explored (Method A, Scheme **2.9**). Secondly, a catalytic version of the reaction was developed (Method B, Scheme **2.9**), where Grignard reagents were still employed, along with substoichiometric amounts of a copper complex. The observed regioselectivity, from both methods, was attributed to coordination of copper to the oxygen atom present in the ynamide (**76**). This coordination results in addition being directed to the β position of the ynamide.

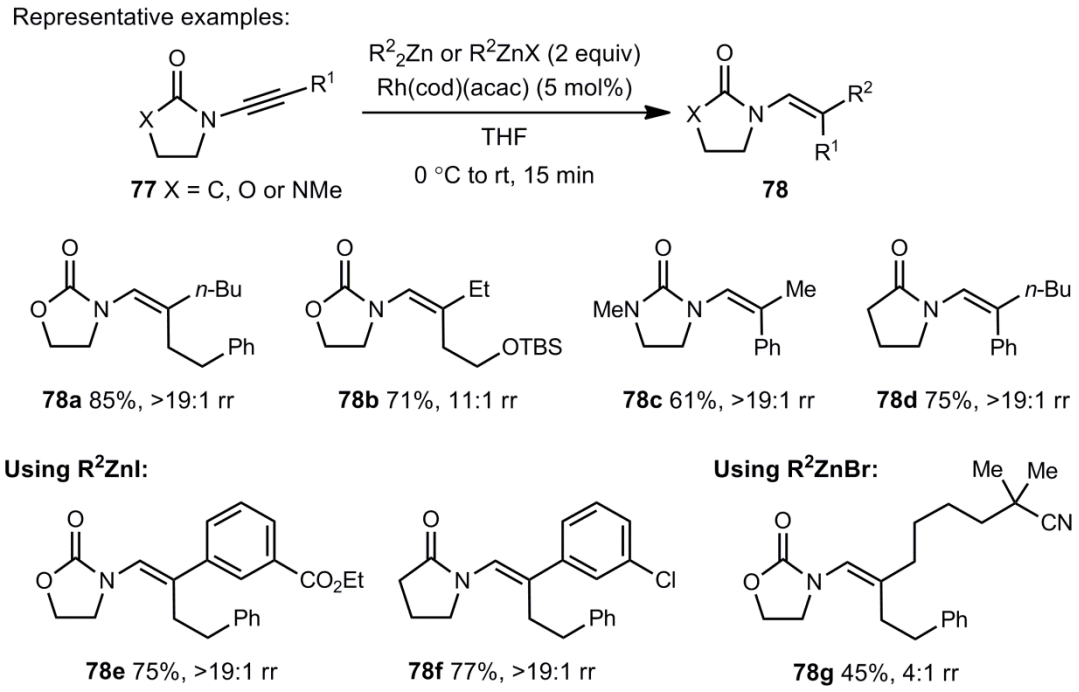


Scheme 2.9

Carbometalation occurred successfully with both alkyl and phenyl reagents (**75a-d**); however, only a small number of ynamides were investigated in this study.

Carbometalation of the ynecarbamates occurred more readily than for ynesulfonamides, hence the ynesulfonamide reactions of Method A required warming to room temperature. The difference in the relative reaction rates is likely due to the comparatively reduced electron density in the triple bond of ynecarbamates, making them more reactive than ynesulfonamides. Development of Method B was an improvement as such low temperatures are not required, and often higher yields of the desired of β,β-disubstituted enamides (**75a**, **75d**) were obtained.

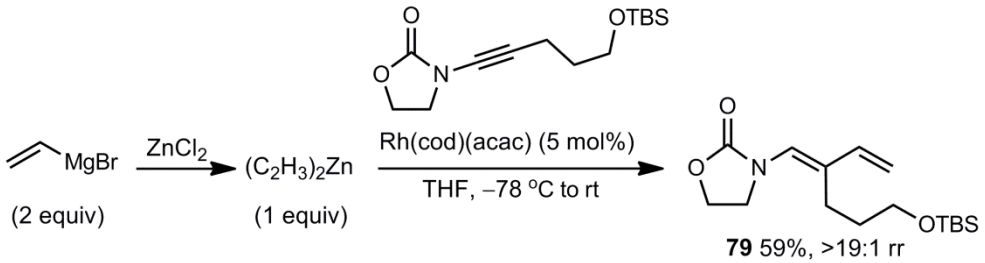
Marek and co-workers have established a good foundation for the carbometalation of ynamides. However, only a small number of ynamides were used and the newly added substituents consisted only of alkyl or phenyl groups, with no additional functionality present. Lam and co-workers have since published work on the carbometalation of ynamides using organozinc reagents and rhodium catalysis (Scheme **2.10**).[33] This improved procedure does not require extreme temperatures and the authors demonstrated the use of a greater variety of ynamides. Additionally, both diorganozinc reagents and organozinc halides were suitable for use in the reaction. This use of organozinc halides expanded the pool of enamides obtained and enabled the inclusion of functional groups such as esters (**78e**) and nitriles (**78g**). The inclusion of such sensitive groups would not be possible in any carbometalations involving more reactive Grignard reagents.



Scheme 2.10

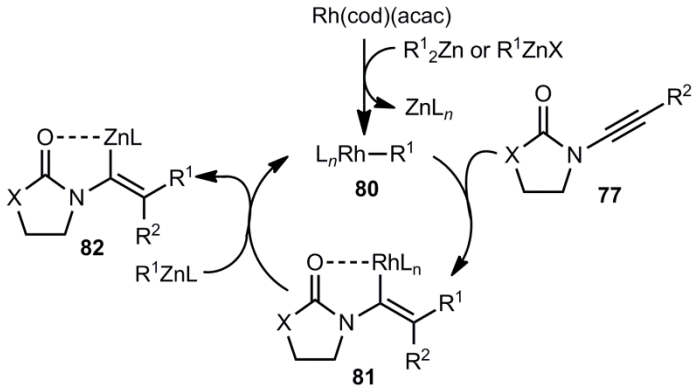
A variety of β,β-disubstituted enamides were isolated in good yields, as single isomers (**78a-f**). Regioselectivity was high, with only one regioisomer being detected in the crude ^{1}H NMR spectrum in most cases. In the case of **78b**, the regioselectivity was slightly reduced, perhaps due to the additional oxygen atom causing some interference in rhodium coordination to the ynamide carbonyl oxygen (see Scheme **2.12**). The yield of enamide **78g** was disappointingly low, due to a competing ynamide hydrometalation pathway.

A further expansion of reaction scope was achieved by using diorganozinc reagents generated from Grignard reagents and zinc chloride (Scheme **2.11**). This procedure resulted in the inclusion of vinyl, benzyl, and various aryl groups (for example **79**).



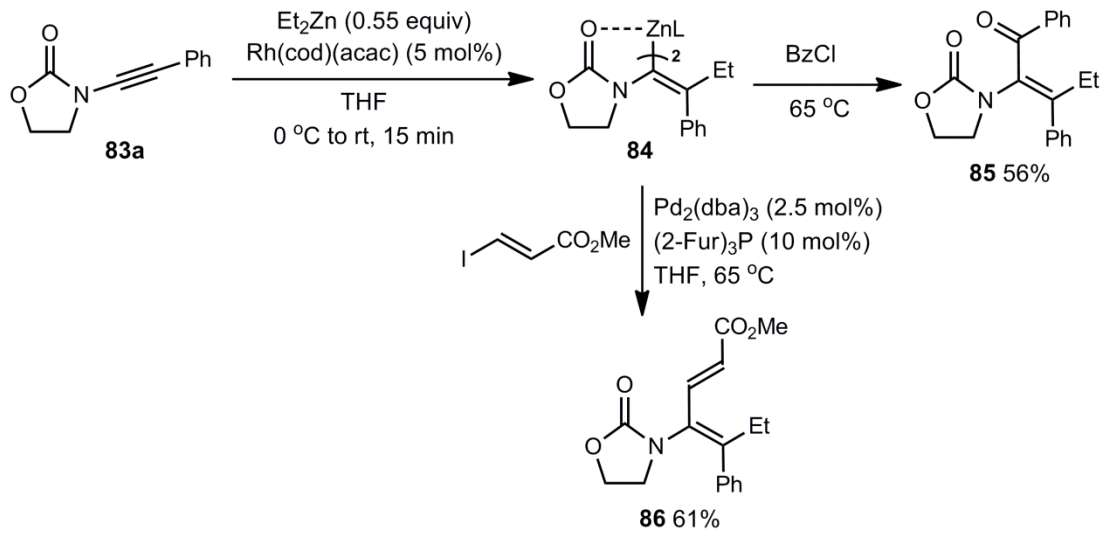
Scheme 2.11

A mechanism was proposed for the reaction (Scheme **2.12**) where firstly transmetalation occurs, to give organorhodium species **80**. The ynamide then undergoes *syn*-carbometalation with **80**, to produce **81**. Prior coordination of rhodium species **80** to the ynamide carbonyl group is believed to be responsible for the regioselectivity of the reaction. Intermediate **81** then undergoes transmetalation with zinc, regenerating the rhodium catalyst, and producing alkenylzinc intermediate **82**, which is protonated upon work-up to provide the enamide.



Scheme 2.12 – Drawn as specified in the relevant publication[33]

The alkenylzinc intermediates that are generated can be further elaborated *in situ* to form tri-substituted enamide products (Scheme **2.13**). Reaction of this intermediate (**84**) with electrophiles such as benzoyl chloride or in cross-coupling Negishi reactions can be successfully carried out (**85**, **86**).

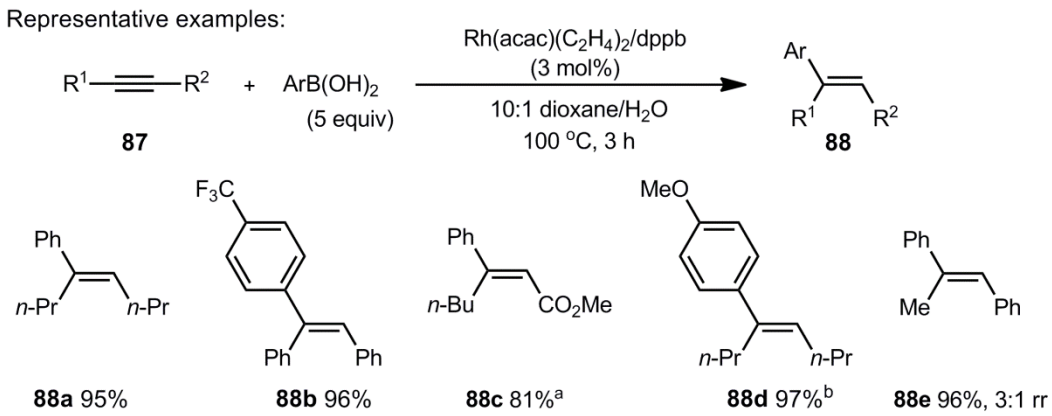


Scheme 2.13

Following the success of carbozincation, it was hoped that similar methodology could be used for the carbometalation of ynamides using organoboron reagents. Use of organoboron reagents would be advantageous as they allow the presence of a greater range of sensitive functional groups and they do not require the strictly anhydrous conditions necessary for use of organozinc reagents.

2.1.5 Addition of Organoboron Reagents to Alkynes

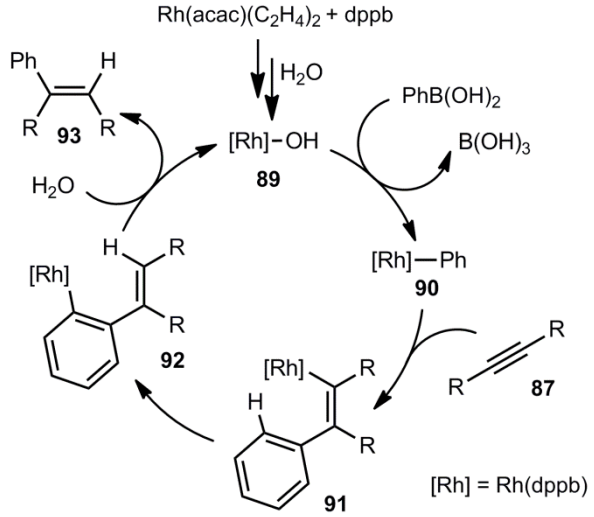
There is literature precedent supporting carbometalation of ynamides using organoboron reagents in the form of addition of organoboron reagents to alkynes. This hydroarylation of alkynes has been developed with nickel,[54] rhodium,[55] palladium,[56] copper,[57] and cobalt catalysis;[58] however, the use of unsymmetrical alkynes remains challenging. In 2001, Hayashi reported the first hydroarylation of internal alkynes with organoboron reagents.[55a] This method used rhodium catalysis and provided a novel route to trisubstituted alkenes (Scheme **2.14**). The alkenes were obtained as the *E* isomer (**88**), which strongly implies that the alkyne substrates underwent *syn*-carbometalation. A number of alkynes were used in this publication; however, most were symmetrical alkynes, thus regioselectivity issues were avoided.



[a] Dppf ligand was used. [b] Reaction carried out at 60 °C, using (4-MeOPhBO)$_3$ instead of boronic acid.

Scheme 2.14

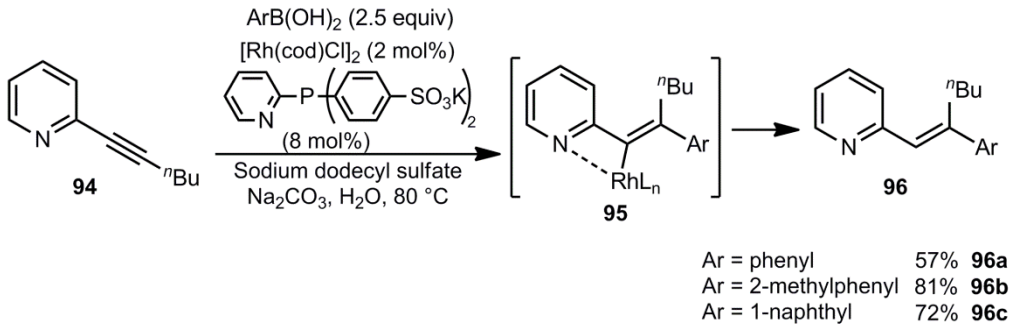
The majority of the reactions were very high yielding (**88a-e**). Both *p*-methylphenyl and *p*-trifluoromethylphenylboronic acids (**88b**) were used successfully; however, a low yield was obtained from use of *p*-methoxyboronic acid or the corresponding boroxine. It was thought that these low yields were due to rapid hydrolysis to anisole at the high reaction temperature, and indeed carrying out the reaction at a lower temperature (**88d**) gave an excellent yield. A single product (**88c**) was obtained from an alkynoate, with the phenyl group selectively adding β to the ester; however, an unsymmetrical alkyne with substituents insufficiently different in sterics or electronics reacted with poor regioselectivity (**88e**). The proposed mechanism is shown in Scheme **2.15**.



Scheme 2.15 – Drawn as proposed in the relevant publication[55a]

It has been proposed that a rhodium hydroxide species (**89**) forms, which promotes transmetalation of the boronic acid. Arylrhodium intermediate **90** then adds to the alkyne in a *syn* fashion (**91**). Hayashi and co-workers found, through deuterium labelling (see Scheme **2.23**), that alkenylrhodium intermediate **91** undergoes a 1,4-rhodium shift, resulting in **92**. Protonation then releases the desired product. Overall, this hydroarylation is a successful initial method, with high stereocontrol as a result of *syn* addition occurring. However, the high regioselectivity of the reaction is not universal and methods that can provide a single product when using unsymmetrical alkynes are required.

One solution for controlling regioselectivity during the hydroarylation of unsymmetrical alkynes was published by Lautens and co-workers.[55b] A rhodium-catalysed reaction of alkynylazaarenes with arylboronic acids had been developed (Scheme **2.16**), using aqueous conditions and a water-soluble ligand. Regioselective addition of the aryl group was achieved through the presence of a 2-pyridyl directing group.



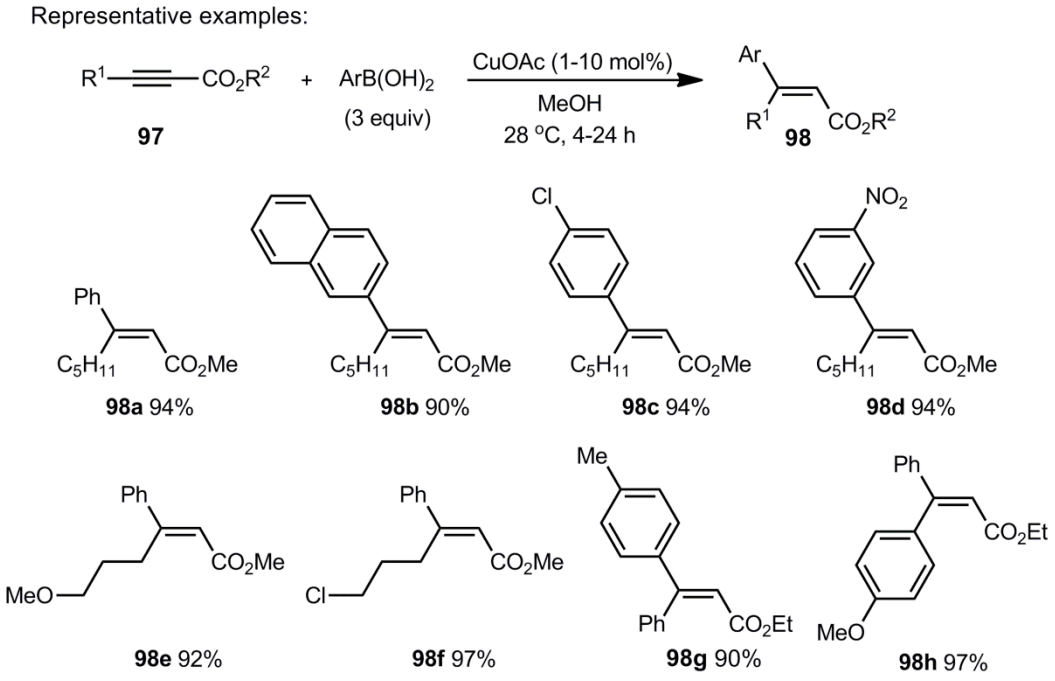
Scheme 2.16

A number of arylboronic acids reacted well with alkyne **94**, with high regioselectivity occurring in each case, due to the presence of the 2-pyridyl moiety. Those boronic acids containing an *ortho* substituent resulted in the highest yields (for example **96b**); most likely due to less protodeboronation occurring with these more hindered boronic acids. Some other successful alkynes, all including a 2-alkynylazaarene motif, were also reported. Mechanistically, coordination of the nitrogen atom of the substrate to rhodium results in regiocontrolled addition of the

aryl group to the alkyne, giving alkenylrhodium complex **95**. Overall, this method presents a directing group approach to hydroarylation and a reaction free from organic solvents, but the substrate scope is limited and the yields are lower than the yields reported in Hayashi's publication.[55a]

In general, the rhodium-catalysed hydroarylation of alkynes has advantages over other methods for the formation of trisubstituted alkenes, namely high *syn*-selectivity and high efficiency. However, to date this rhodium-catalysed reaction is only applicable to arylboronic acids and certain internal alkynes.

Yamamoto demonstrated the use of less expensive copper catalysis and milder, simplified reaction conditions.[57] In this method, arylboronic acids underwent copper(I) acetate catalysed addition to alkynoates, and *syn*-hydroarylation products were obtained in high regioselectivity.



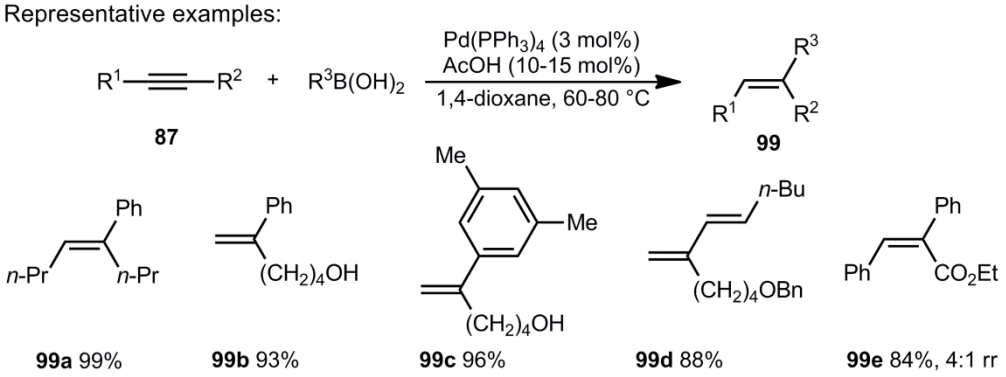
Scheme 2.17

Using methyl 2-octynoate, the boronic acid scope was extensively explored. Many arylboronic acids provided an excellent yield, with high regio- and stereoselectivity occurring (for example **98a-d**). A higher catalyst loading of 10 mol% had been

required in the case of **98d**, in order to obtain the high yield. Unfortunately, use of *p*-methoxyphenylboronic acid was unsuccessful, due to homocoupling of the boronic acid occurring, and both heteroarylboronic acids and *n*-pentylboronic acid did not undergo the reaction. In the case of alkylboronic acids, β-hydride elimination is perhaps responsible for their poor reactivity.

Further studies showed that both alkyl- and aryl-substituted alkynoates are well tolerated in the reaction (**98e-h**), giving a single isomeric product in high yield. However, a terminal, trimethylsilyl-substituted or brominated alkynoate were not suitable substrates. Methanol was found to be a critical component of the reaction, and it is believed that methanol both activates the boronic acid towards transmetalation and acts as a protic source for the alkenyl-copper intermediate, to release the desired alkene product. Overall, Yamamoto's group have produced a mild and inexpensive method for alkynoate hydroarylation, and have demonstrated that alkynoates can undergo regioselective addition.

Another transition metal that has been used for the hydroarylation of alkynes is palladium. The first palladium-catalysed example was published by Oh and co-workers in 2003.[56a] This publication has also included the use of previously elusive terminal alkynes and alkenylboronic acids. High yields and regioselectivities were observed in the majority of the reactions (Scheme **2.18**).



Scheme 2.18

Symmetrical aliphatic alkynes and terminal alkynes were successfully utilised (**99a-d**), but surprisingly, the use of alkynoates resulted in low regioisomeric ratios (**99e**) and the products were isolated as a regioisomeric mixture. In contrast to other hydroarylation methods, the successful use of alkenylboronic acids was reported (for example **99d**). This method has broadened the scope of alkyne hydroarylation through the inclusion of additional substrate classes, but the use of unsymmetrical internal alkynes had little success.[56c]

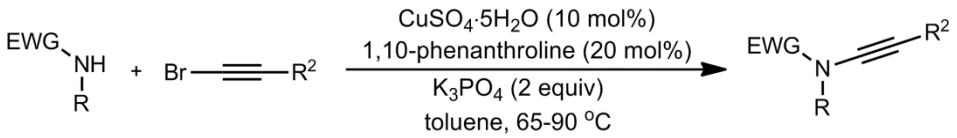
It can be concluded that the carbometalation of alkynes using organoboron reagents is very successful with certain substrates, but control of regioselectivity can be a significant problem and not all boronic acids perform well. High regioselectivities are usually observed when there are substantial differences in the steric and/or electronic properties of the two substituents attached to each end of the alkyne. Use of a directing group within the substrate is another tactic for controlling regioselectivity. It was hoped that when utilising ynamides, a known directing effect of the carbonyl group, namely binding of the metal catalyst, would impart a high level of regiocontrol.

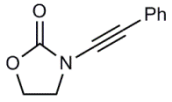
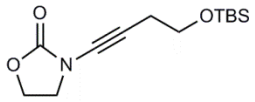
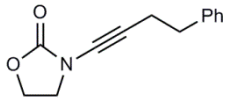
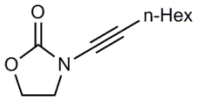
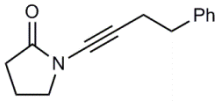
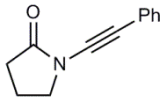
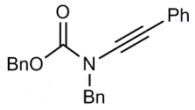
2.2 Results and Discussion[59]

2.2.1 Preparation of Ynamides

For the carbometalation of ynamides to be explored, synthesis of a small ynamide library was first required. Within the Lam group, most synthesis of ynamides is carried out using a procedure by Hsung and co-workers (see Chapter **1.1**).[8] This procedure uses bromoalkynes in a copper-catalysed coupling reaction, with amides or other appropriate nitrogen-containing substrates. The ynamides that were synthesised, for further investigation, based on this method are shown in Table **2.1**.

Table 2.1: Synthesis of Ynamides



Ynamide	Structure	Temp (°C)	Time (h)	Yield
83a[b]		65	17	58%
83b		65	67	15%
83c		65	23	64%
83d[c]		90	36	56%
83e[a,b]		65	23	31%
83f		65	48	19%
83g		80	24	47%

[a] 20 mol% $CuSO_4 \cdot 5H_2O$ was used. [b] 4 Å MS were used. [c] 20 mol% anhydrous $CuSO_4$ was used.

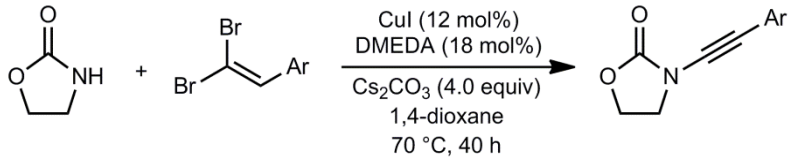
The synthesis of ynamides is known to be capricious[60] and often results in lower yields than expected from the literature precedent. The yield of **83f** was disappointing based on Hsung's results,[8] but ynamides **83a-e** were successfully synthesised in comparable or improved yields with respect to previously published results by our group.[33] Known causes of lowered yields when utilising copper-mediated coupling protocols for ynamide synthesis include the use of inferior quality K_3PO_4 and undesired consumption of the bromoalkyne through homocoupling of this reagent, producing 1,3-diynes.[8,60] It is thought that this side reaction had occurred to a minor extent (5-10% conv) during some of the reactions reported in Table **2.1** (**83a**, **83d**, **83f**), thus slightly lowering the available yield. However, for all of the reactions from Table **2.1**, the majority of the remaining mass balance consisted of starting materials.

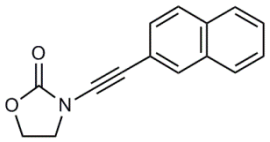
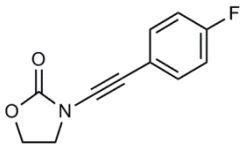
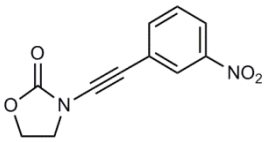
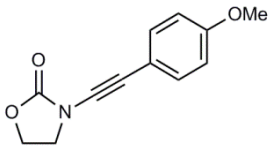
Using 20 mol% of the copper catalyst resulted in the yields of **83d** and **83e** being significantly improved on that previously reported.[33] This increase in catalyst loading could in future be applied to ynamides **83b** and **83f** in order to improve the yields obtained. Anhydrous $CuSO_4$ as the catalyst was briefly investigated (for example **83d**) in an attempt to further increase the yield, by decreasing any possible side product formation from hydration of the ynamide to an imide. However, the yields from these reactions were found to be comparable with reactions using $CuSO_4 \cdot 5H_2O$, and no significant benefit was observed. An increased reaction temperature was found to be beneficial in some cases (**83d**, **83g**), whereas, for all of the ynamides, extending the reaction time beyond 24 hours did not appear to improve the yield.

In general, lower yields of pyrrolidinone-based ynamides are obtained than when synthesising their oxazolidinone equivalents. The lower yields may possibly be a result of an increased susceptibility of pyrrolidinone-based ynamides towards hydration of the triple bond, or perhaps more simply a lower reactivity of the 2-pyrrolidinone starting material in comparison to 2-oxazolidinone. In Table **2.1**, ynamide **83e** was obtained in a 31% yield, but a publication by Evano and co-workers reported the yield of this ynamide to be 80%.[10] The procedure of Evano and co-workers involves the copper-catalysed coupling of the relevant nitrogen component with a dibromoalkene. In future, ynamide **83e** could be synthesised using the Evano method in the hope of increasing the yield.

The procedure of Evano and co-workers[10] was used to synthesise additional ynamides **83h-k**. This coupling method uses catalytic copper iodide and dibromoalkene substrates, which can be made from the corresponding aldehyde. The ynamides synthesised using the Evano method are detailed in Table **2.2**.

Table 2.2: Further Synthesis of Ynamides



Ynamide	Structure	Yield
83h		12%
83i		30%
83j		28%
83k		53%

The yields of ynamides **83h-j** were lower than had been anticipated when using this method; however, these ynamides (**83h-j**) were not previously known in the literature so their preparation was considered beneficial despite the low yield. Ynamide **83h** was originally isolated by column chromatography in a more respectable 38% yield, but was found to be insufficiently pure due to minor imide contamination, and subsequent recrystallisation of the product resulted in a drastically reduced yield.

Since the synthesis of ynamides **83h-k** was conducted, a publication by Mizuno and co-workers[12] has reported the synthesis of **83i** in a greatly improved 88% yield. This coupling method, which uses a copper(II) hydroxide catalyst, should be explored for future ynamide synthesis.

Further ynamides mentioned in this study, which were synthesised by other members of the Lam group, are shown in Figure **2.4**.

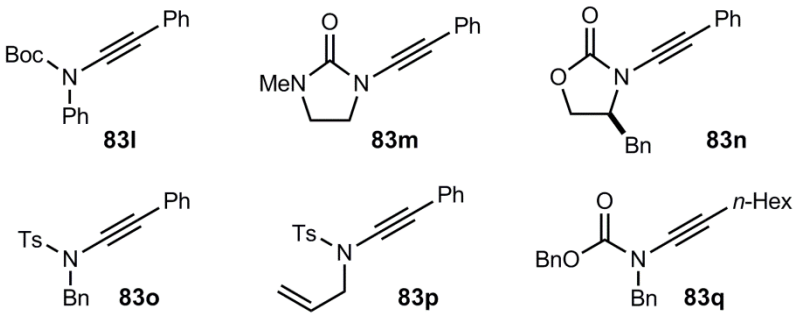
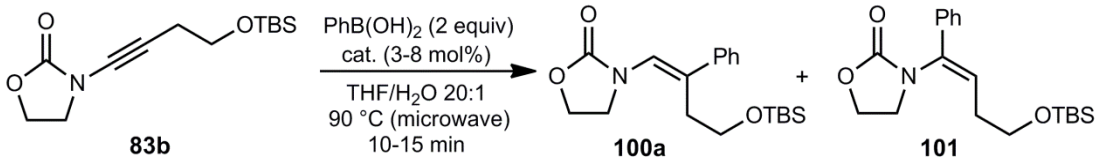


Figure 2.4

2.2.2 Optimisation of the Carbometalation Reaction

To initiate the investigation into the carbometalation of ynamides using organoboron reagents, pre-catalyst screening was carried out, in collaboration with Lam group member Benoit Gourdet. Ynamide **83b** and phenylboronic acid were used as a model reaction for initial studies and a summary of the screening results is shown in Table **2.3**.

Table 2.3: Carbometalation Screening Reactions



83b **100a** **101**

Entry	Pre-catalyst	L/Additive	Result
1*	Rh(cod)(acac)	-	Complex mixture of products
2*	$[Rh(cod)Cl]_2$	-	Complex mixture of products
3*	$Rh(acac)(C_2H_4)$	dppb	No reaction
4*	$[Rh(cod)(MeCN)_2]BF_4$	-	Complete conversion >19:1 ratio of **100a**:**101**
5[a]	$Pd(OAc)_2$	Na_2CO_3 (2 equiv)	79% conversion 5:1 ratio of **100a**:**101**
6	$Pd(OAc)_2$	Na_2CO_3 (2 equiv)	25% conversion 8:1 ratio of **100a**:**101**
7*, [b]	CuOAc	-	Complete conversion 4:1 ratio of **100a**:**101**
8[a]	$Co(acac)_2 \cdot H_2O$	-	No reaction
9	$Pd(PhCN)_2Cl_2$	K_2CO_3 (1.3 equiv)	≥70% conversion 6:1 ratio of **100a**:**101**

[a] Reaction was conducted at room temperature for 18 h, with 1,4-dioxane in place of THF. [b] Reaction was conducted at room temperature for 2 h.

Firstly, the use of rhodium was explored. With the previously reported catalyst for carbozincation of ynamides,[33] Rh(cod)(acac), no conversion occurred at room temperature and a complex mixture of products resulted when the reaction was carried out at 90 °C under microwave irradiation (entry 1). Similar results were obtained with $[Rh(cod)Cl]_2$ (entry 2). Conditions based on those developed by Hayashi[55a] (entry 3) were ineffective for our carbometalation reaction, with only starting materials being recovered. Whereas, employment of a cationic rhodium complex, $[Rh(cod)(MeCN)_2]BF_4$, provided the desired product with high regioselectivity (entry 4). At room temperature, three days had been required for complete conversion to occur, but at 90 °C, under microwave irradiation, the reaction was successful.

* These reactions were carried out by Benoit Gourdet.

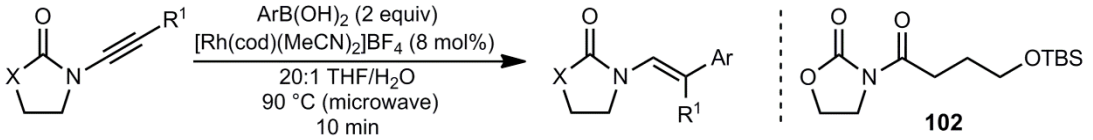
Acceptable conversion to the desired enamide was obtained using $Pd(OAc)_2$ (7 mol%) along with Na_2CO_3 (entry 5), but only moderate regioselectivity occurred. Reduction of the catalyst loading to 3 mol% combined with microwave heating, led only to low conversion (entry 6). An efficient pre-catalyst was found in CuOAc as complete conversion occurred at room temperature (entry 7), but the regioselectivity was poor. Employment of a cobalt(II) species (entry 8) resulted in no reaction of the ynamide, however use of a phosphine ligand with this catalyst may be necessary.[58] Conditions similar to those developed by Larock[61] (entry 9) provided a fairly good conversion to the desired enamide, but a messy crude reaction mixture and moderate selectivity ratio also resulted. Therefore, pre-catalysts based on palladium or copper gave some success, but it was concluded that $[Rh(cod)(MeCN)_2]BF_4$ was the most appropriate pre-catalyst for the proposed carbometalation reactions.

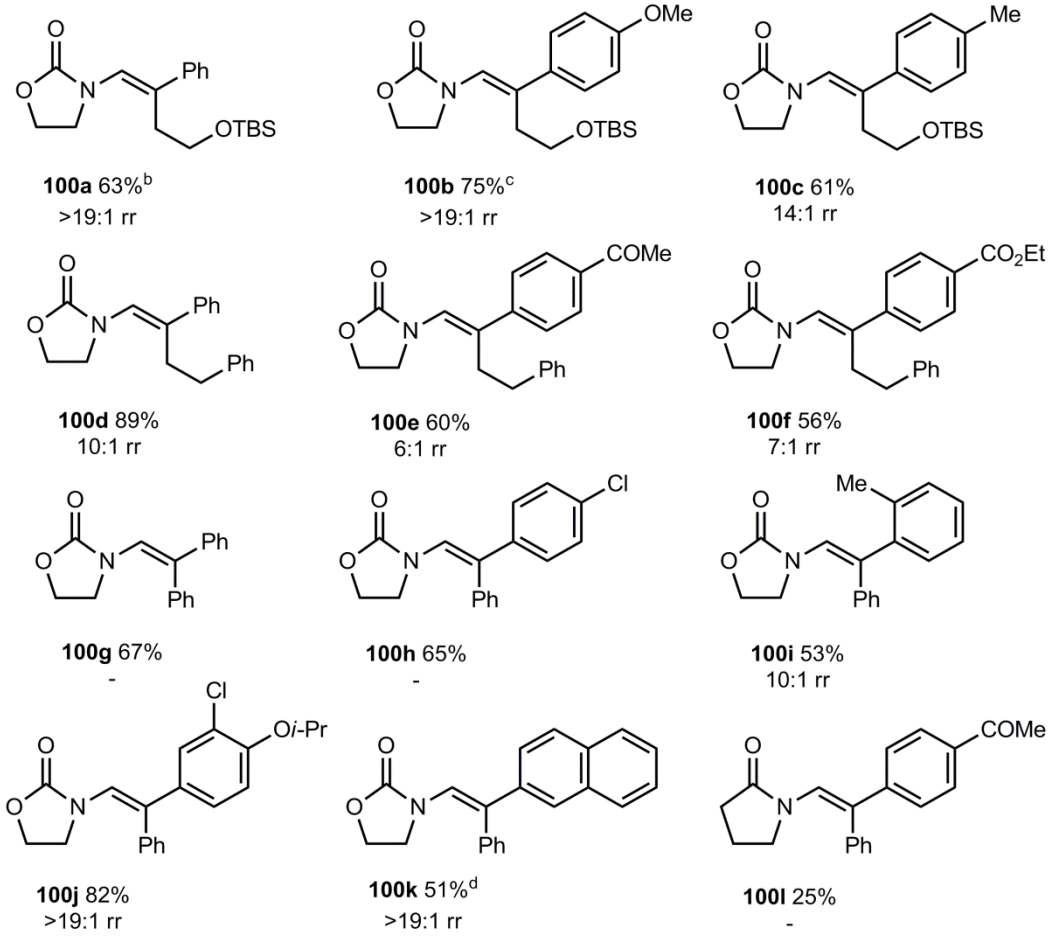
With the chosen pre-catalyst now in hand, lowering of the 8 mol% catalyst loading used in entry 4 was desired. Unfortunately, both significantly longer reaction times and poor conversions were encountered when the catalyst loading was lowered. Additionally, superior conditions could not be achieved through variation of the organic solvent component. It was found that use of 1,4-dioxane resulted in very low conversions and use of methanol resulted in a mixture of isomeric carbometalation products being produced. When a reaction was conducted using aqueous sodium hydroxide as the water component of the solvent mixture, very little conversion to the desired product occurred. Therefore, the reaction conditions used in entry 4, Table **2.3** were employed and a study of the reaction scope initiated.

2.2.3 Carbometalation of Ynamides Using Boronic Acids

Using the optimised conditions shown in Table **2.4**, my collaborator Benoit Gourdet successfully carried out a number of carbometalation reactions, using oxazolidinone-based ynamides and a variety of arylboronic acids.

Table 2.4: Ynamide Carbometalation with Arylboronic Acids[a,*]





[a] Reactions were carried out on a 0.4 mmol scale. Unless otherwise indicated, cited yields are of isolated major regioisomers. rr = regioisomeric ratio as determined by ^{1}H NMR analysis of the unpurified reaction mixtures. [b] Isolated as an 8:1 inseparable mixture of **100a** and **102**. Cited yield has been adjusted to reflect impurity. [c] Isolated as a 16:1 inseparable mixture of **100b** and imide **102**. Cited yield has been adjusted to reflect impurity. [d] Reaction was carried out on 1.0 mmol scale.

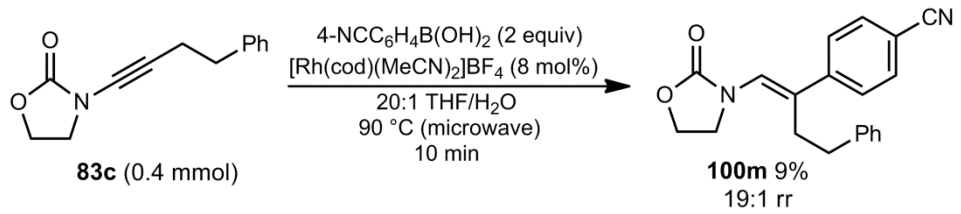
The results (Table **2.4**) show that oxazolidinone-based ynamides containing either aromatic or aliphatic substituents were successful substrates for the carbometalation reaction. Although ynamide **83b** underwent the reaction successfully (**100a-c**), some hydration of the ynamide to imide **102** occurred. Unfortunately, this imide was inseparable from desired products **100a** and **100b**, by chromatography. Reaction of pyrrolidinone-containing ynamide **83f** resulted in a mixture of products being obtained, and thus enamide **100l** was isolated in low yield. In general, pyrrolidinone

[*] These reactions were carried out by Benoit Gourdet.

ynamides tended to undergo hydration of the triple bond rather than the desired carbometalation reaction. Additionally, ynamide substrates where the nitrogen atom is not part of a cyclic system, such as **83l**, were not included in the above results as although carbometalation occurred, regioselectivity of the reaction was negligible. With regards to the boronic acid scope, a variety of aryl substituents and substitution patterns were well tolerated in the reaction (for example **100e** and **100j**). Generally, an electron-rich boronic acid resulted in a higher yield and regioselectivity than if a boronic acid containing an electron-withdrawing substituent was used (**100b** and **100d** *vs* **100e** and **100f**). The presence of an *ortho*-substituent on the boronic acid (**100i**) resulted in only a slight reduction in yield.

In many cases, the yields reported in Table **2.4** are not as high as would be anticipated from the good conversions of the ynamides that occurred. On closer examination, side reactions, largely ynamide hydration, were an issue, except with the most reactive of substrate combinations (**100d**, **100j**). Thus lowered yields resulted. In retrospect, increasing the equivalents of boronic acid used or lowering the reaction temperature may have improved the yield, by favouring carbometalation over ynamide degradation.

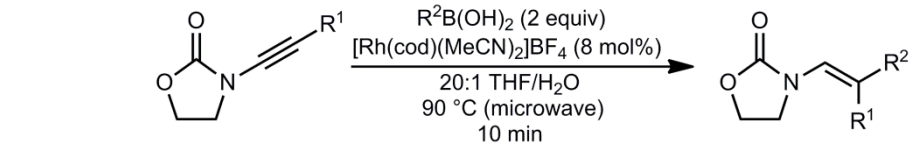
A small number of boronic acids were found not to be suitable for carbometalation, including pentafluorophenyl boronic acid and *p*-cyanophenyl boronic acid. It is assumed that these boronic acids are not sufficiently nucleophilic for the desired reaction to occur. For *p*-cyanophenylboronic acid, reaction with a number of different ynamides was tried, but none provided sufficient conversion to the desired product. The reaction in Scheme **2.19** resulted in a complex product mixture, and enamide **100m** was isolated in only a very low yield.

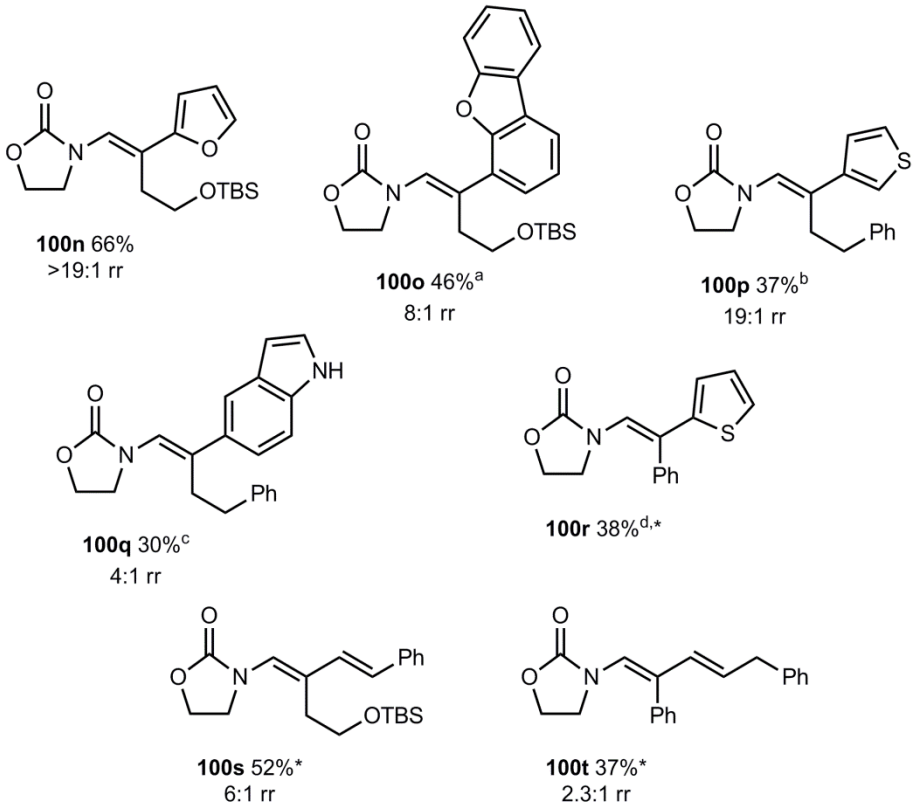


Scheme 2.19

Having produced a number of successful reactions using aryl boronic acids (Table **2.4**) we wanted to investigate heteroaromatic and alkenyl boronic acids under the standard reaction conditions. Some of these results are shown in Table **2.5**.

Table 2.5: Carbometalation with Heteroaryl and Alkenyl Boronic Acids[a]



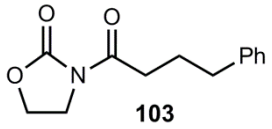


[a] Reactions were carried out on a 0.4 mmol scale. Unless otherwise indicated, cited yields are of isolated major regioisomers. rr = regioisomeric ratio as determined by ^{1}H NMR analysis of the unpurified reaction mixtures. [a] Isolated as 13:1 inseparable mixture of product and imide **102**. [b] Reaction was conducted without added H_2O. [c] Isolated as 9:1 inseparable mixture of product and regioisomer. [d] Regioisomeric ratio could not be accurately determined. Reaction was carried out on 2.0 mmol scale.

A good yield of the desired enamide was obtained when using furanyl-2-boronic acid (**100n**); however, for the other heteroaromatic boronic acids the yields were moderate (**100o-r**). The lower yield of enamide **100o** was most likely due to the large steric bulk on the boronic acid. For the reaction of thiophene-3-boronic acid with

[*] These reactions were carried out by Benoit Gourdet.

ynamide **83c**, it was found that under the standard reaction conditions a significant amount of side product, believed to be imide **103**, was produced. This imide was also difficult to separate from the desired enamide (**100p**) by column chromatography, thus further reducing the yield. Repetition of the reaction using only THF as the reaction solvent, with no water added to the reaction mixture, almost eradicated the formation of the imide, and resulted in a 37% yield.



103

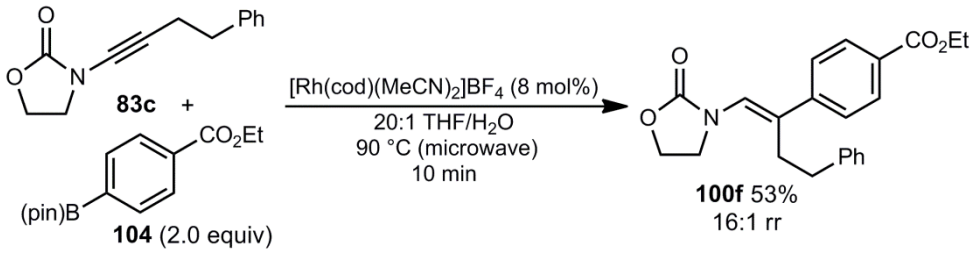
Figure 2.5

Use of thiophene-2-boronic acid resulted in a yield of enamide **100r** similar to that of **100p**. Although significant hydration of the ynamide still occurred in this reaction, separation of the enamide and imide products did not seem to be such an issue. With an indole boronic acid, the regioselectivity was low (**100q**). In this case, it is speculated that the presence of indole NH groups in the reaction mixture may be interfering with coordination of rhodium to the carbonyl oxygen of the ynamide (see mechanism, Scheme **2.22**), and thus resulting in lowered regioselectivity. It also proved difficult to completely separate enamide **100q** from its regioisomer; hence, the product was isolated as a mixture, in a modest yield.

Gratifyingly, alkenyl boronic acids were adequate reagents for carbometalation (**100s** and **100t**). However, regioselectivity was particularly poor in the synthesis of enamide **100t**, resulting in a low yield. The corresponding regioisomer was isolated in 9% yield in this case.

2.2.4 Carbometalation of Ynamides using Other Organoboron Reagents

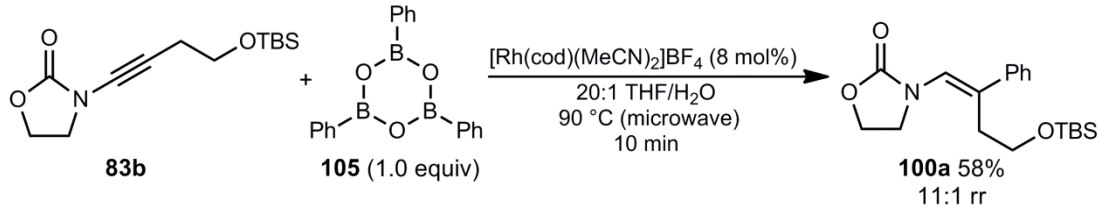
It was then demonstrated that other organoboron reagents, such as boronic esters and triarylboroxines, can be used successfully. In an example of this scope expansion, ynamide **83c** was reacted with a boronic ester (Scheme **2.20**).



Scheme 2.20*

The above reaction resulted in a much improved regioselectivity ratio compared with using the corresponding boronic acid (Table **2.4**); however, a higher level of impurities also resulted. Consequently, enamide **100f** was obtained in a comparative yield to that in Table **2.4**. It could be advantageous to apply the use of a pinacol boronic ester to the reactions in Table **2.5**, to establish if an increase in regioselectivity can also be achieved in these cases.

An example utilising triphenylboroxine (**105**) also successfully produced a similar yield as to when the corresponding boronic acid had been utilised (Scheme **2.21**).



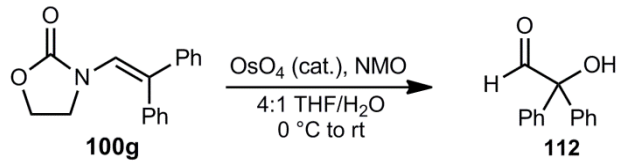
Scheme 2.21*

* These reactions were carried out by Benoit Gourdet.

An organoboron reagent that was found to be unsuccessful under the developed reaction conditions was potassium phenyltrifluoroborate. This reagent resulted in an unidentifiable mixture of products being obtained.

2.2.5 Regio- and Stereochemical Determinations

The regiochemical outcome of the carbometalation reaction between ynamide **83a** and phenylboronic acid was determined through dihydroxylation of enamide **100g.**



Scheme 2.22[*]

This reaction provided α-hydroxyaldehyde **112** (confirmed by comparison of spectral data with that described in the literature)[62] as the main product, rather than a phenyl ketone, thus confirming the anticipated regiochemistry. The identities of the other products from carbometalation of ynamide **83a** were assigned by analogy. The regiochemistry of the products from carbometalation of an alkyl-substituted ynamide can be determined directly from the alkene region of the ^{1}H NMR spectra. When the alkene proton signal is a singlet this confirms the product is β,β-disubstituted, if the carbometalation reaction had produced an α-substituted enamide then the alkene signal would be a triplet.

The stereoselectivities of the carbometalation reactions producing enamide products **100c**, **100f**, **100l**, and **100s** were determined on the basis of NOESY experiments, which displayed the diagnostic interactions shown in Figure **2.6.**

[*] This reaction was carried out by Benoit Gourdet.

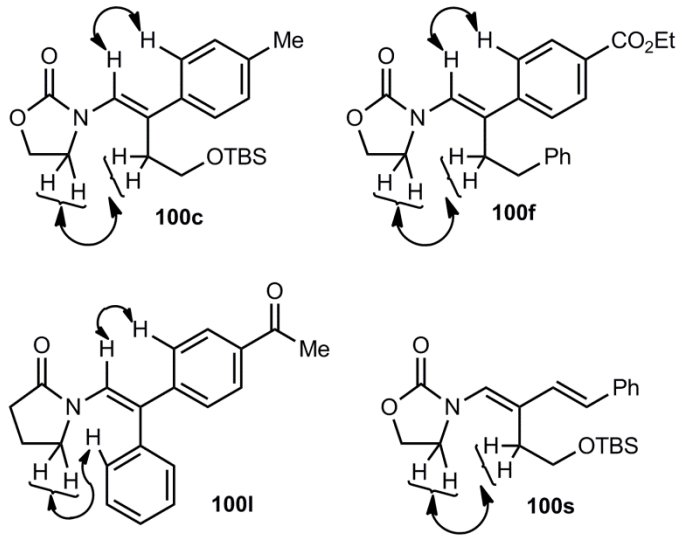
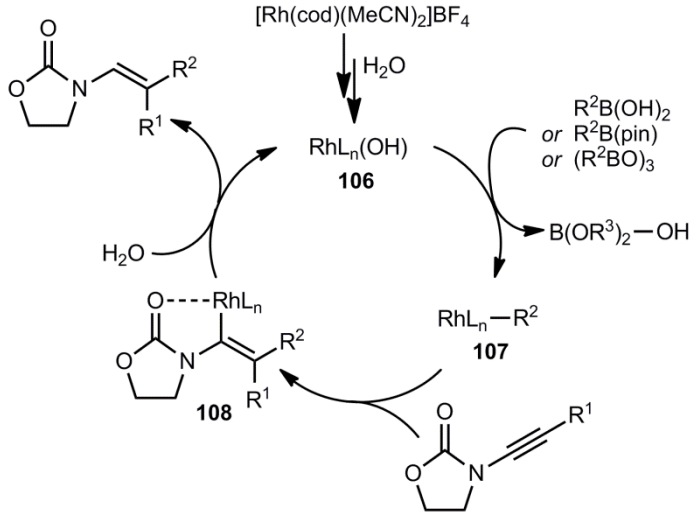


Figure 2.6

The stereochemistry of the remaining carbometalation products were then assigned by analogy.

2.3 Mechanism

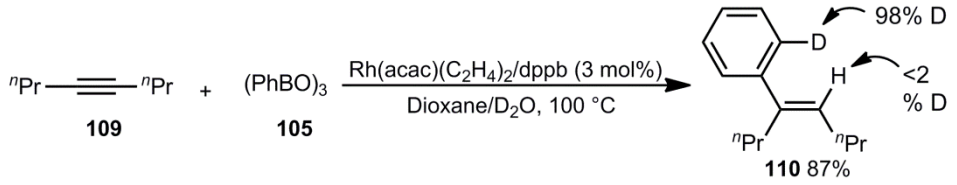
The proposed mechanism for the reaction is shown in Scheme **2.23**.



Scheme 2.23

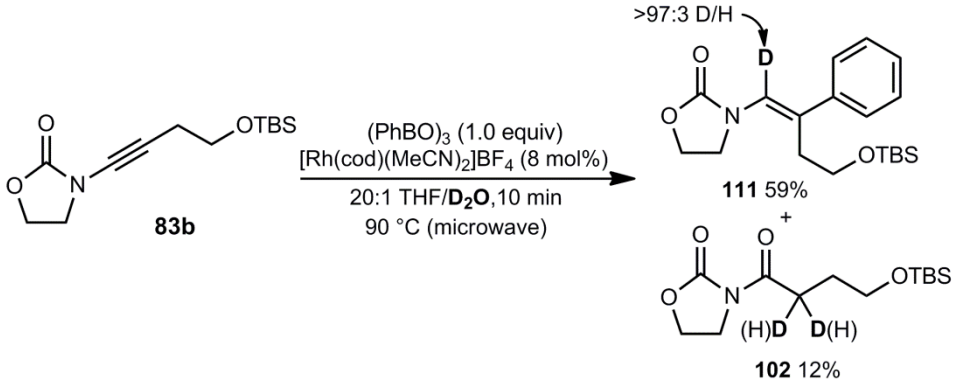
Presumably, as assumed by other groups,[55a-b,55g] a rhodium(I) hydroxide species (**106**) is generated under the reaction conditions. Formation of arylrhodium intermediate **107** would then occur through transmetalation. Intermediate **107** then adds to the ynamide in a *syn*-carbometalation, directed by the carbonyl group. Protonation of rhodium enamide **108** releases the desired product and regenerates the catalytic species (**106**).

In Hayashi and co-workers' publication on the addition of boronic acids to alkynes,[55a] deuterium labelling studies revealed that after carbometalation took place, a 1,4-rhodium migration from the alkenyl position to an *ortho*-position on the aryl group occurred (see Scheme **2.15**). A reaction of alkyne **109** with triphenylboroxine, conducted in D_2O (Scheme **2.24**), provided most of the evidence for this observation.



Scheme 2.24

Within our carbometalation reaction, alkenylrhodium intermediate **108** is presumed to be present and with the aim of understanding the proposed mechanism further, an analogous deuterium labelling experiment was carried out (Scheme **2.25**).



Scheme 2.25[*]

[*] This reaction was carried out by Benoit Gourdet.

Carbometalation of ynamide **83b** was conducted using triphenylboroxine in THF/D_2O. This experiment provided enamide **111** with >97% deuterium incorporation at the alkenyl position, along with a small amount of imide **102** as a mixture of isotopologues. From this study, it was clear that 1,4-rhodium migration does not occur to any considerable extent in our reactions. It is assumed that the further stability conferred onto alkenylrhodium species **108** through binding to the carbonyl group present on the ynamide impedes rhodium migration.

2.4 Conclusions

A method for rhodium-catalysed carbometalation of ynamides has been successfully developed. A range of organoboron reagents can be used, including aryl, heteroaryl, and alkenylboronic acids, arylboronic esters, and triarylboroxines. Although the yields are modest in some cases, the synthesis of multisubstituted enamides in a regio- and stereocontrolled manner has been achieved, which would be challenging by other routes.

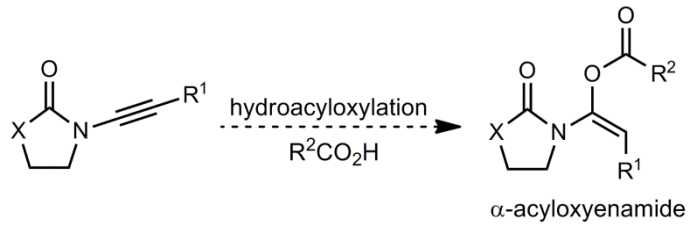
This method is a good complement to the previously published carbozincation of ynamides, and allows even greater functional group compatibility, which broadens the pool of enamides prepared. Additionally, organoboron reagents are readily available, and their stability to air and moisture render them easy to handle. All of these above aspects make this reaction highly attractive for the preparation of multisubstituted enamides.

Further improvement to the described carbometalation of ynamides could perhaps be achieved through re-optimisation of the boronic acid equivalents and reaction temperature used, in order to increase the yields that were obtained. Lowering of the reaction temperature and use of conventional heating may be sufficient to improve some of the reaction yields. Alternatively, if this re-optimisation is insufficient, redesign of the reaction conditions could be attempted, so as to eliminate the requirement for the presence of water. In this situation, hydration of the ynamide would be avoided and consequently higher yields should result. One potential way of

achieving water-free conditions could be to use $[Rh(cod)OH]_2$ in place of the current Rh(I) source, along with methanol as a protic source for the reaction. This alteration would remove the assumed requirement for a L_nRh-OH species to be formed *in situ* before the carbometalation reaction is commenced.

3. Palladium-Catalysed Hydroacyloxylation of Ynamides

Over the past thirty years, the metal-catalysed addition of carboxylic acids to alkynes has been studied extensively.[63] This reaction, with the carboxyl group adding to one end of the alkyne triple bond and a proton to the other, can be termed hydroacyloxylation and results in an enol ester product. Literature precedent shows that significant problems with regio- and stereoselectivity can occur, especially when employing unsymmetrical internal alkynes. The use of ynamides, in place of alkynes, could address this issue as the reaction should occur with high regioselectivity (Scheme **3.1**). This assumption is based on the knowledge that heteroatom nucleophiles usually add regioselectively to the α-carbon of the ynamide,[64] as a result of the polarisation of the ynamide triple bond (as discussed in Chapter 1).



Scheme 3.1

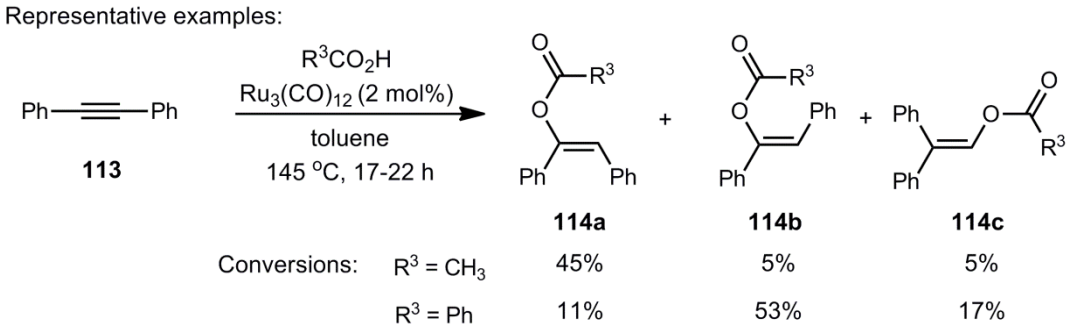
As part of a program developing new applications of ynamides, further investigation of the reactivity of ynamides and development of routes to different enamide structures were desired. Thus, we became interested in hydroacyloxylation. The resulting α-acyloxyenamide derivatives from hydroacyloxylation would be novel compounds and the synthesis of these compounds would expand the pool of available enamide-based structures. It was thought that α-acyloxyenamides would possess useful reactivity for further transformations and the development of the hydroacyloxylation of ynamides would provide a means to investigate the chemistry of these α-acyloxyenamide products.

The synthesis of α-acyloxyenamides in a regio- and stereocontrolled manner through the metal-catalysed hydroacyloxylation of ynamides is described within the following chapter.

3.1 Introduction

3.1.1 Hydroacyloxylation of Alkynes

There are a large number of publications on the addition of carboxylic acids to alkynes. Historically, mercury salts had been used for this addition reaction,[65] but the development of a less toxic and more efficient method was needed. Consequently, Rotem and Shvo published the first metal-catalysed hydroacyloxylation of alkynes, using ruthenium catalysis, in 1983 (Scheme **3.2**).[66] Unfortunately, this early procedure had some drawbacks as a mixture of isomeric products resulted from the reactions and only low conversions were obtained in many cases. Additionally, the reaction was conducted at high temperature, using a sealed reaction vessel, and mostly symmetrical alkynes were used.



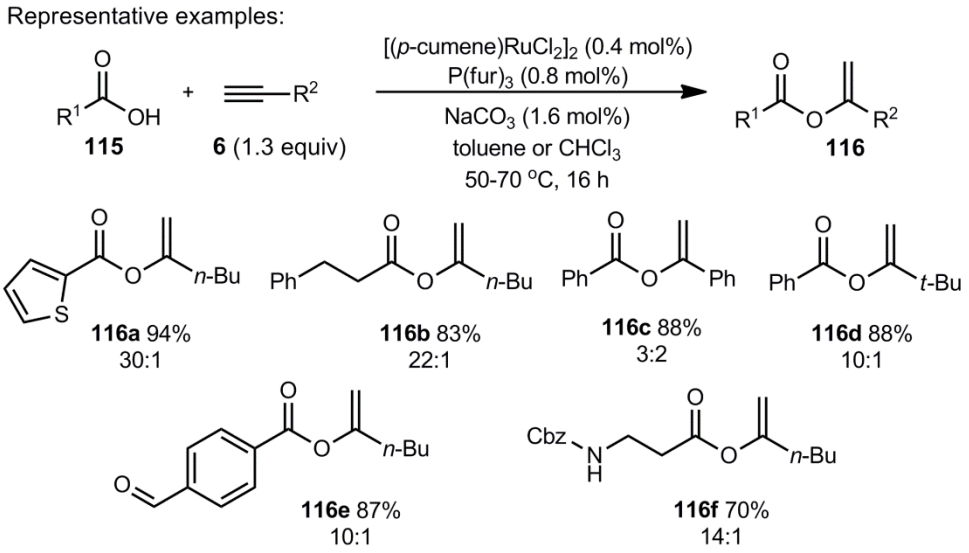
Scheme 3.2

For the addition of acetic acid to **113**, conversion was moderate and mostly the *E*-enol ester (**114a**) was produced. Conversely, reaction with benzoic acid resulted in the *Z*-enol ester (**114b**) being predominant and the conversion was much improved. In both cases, a small proportion of unexpected rearrangement product **114c** was also obtained. This pioneering method provided a much more favourable route to enol

esters than using stoichiometric mercury, but there is much scope for improvement, in both conversion and control of the isomeric product distribution.

Many other catalytic procedures have since been developed, mostly using ruthenium, but successful methods involving unsymmetrical internal alkynes are rare. Impressively, for terminal or symmetrical alkynes the reaction can now be tuned to produce the desired enol ester isomer, simply by selecting the appropriate ruthenium pre-catalyst and ligand.

Gooβen and co-workers described the selective production of two different enol ester isomers, through the use of two ruthenium catalyst system variants.[67] The two methods are more favourable than the majority of previously published procedures for the hydroacyloxylation of alkynes, as commercially available, air-stable catalysts and reagents are employed. The first catalytic system developed provides a Markovnikov enol ester from terminal alkynes (Scheme **3.3**), using a phosphine ligand and very low catalyst loadings.

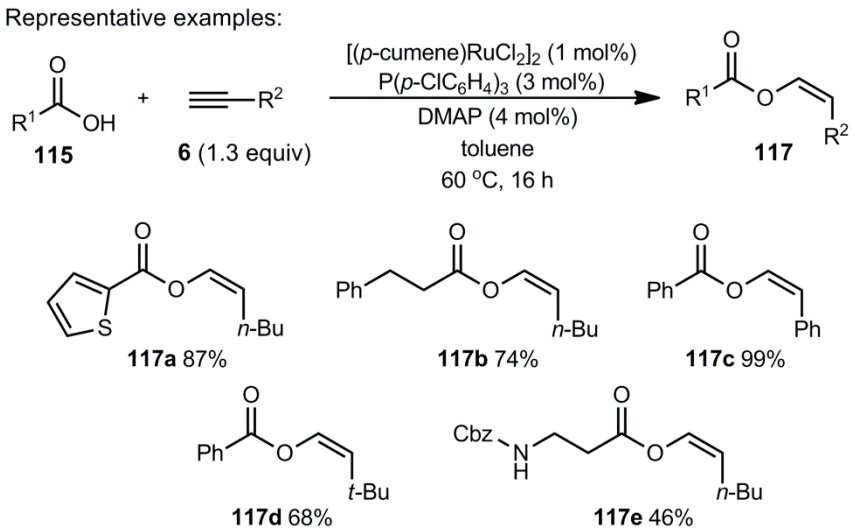


Scheme 3.3

A wide range of carboxylic acids were explored (**116a-f**), but only a small selection of alkynes were demonstrated. The products were produced in high yield; however, the isomeric ratio of the isolated product was variable. Here, the ratio refers to the

Markovnikov product (**116**) versus the *Z-anti*-Markovnikov product (see Scheme **3.3**). The majority of the published examples had an excellent product ratio (**116a**, **116b**), but the use of a bulky *t*-butyl substituted alkyne caused the selectivity to decline (**116d**) and a poor ratio of products was obtained when phenylacetylene was employed (**116c**).

Exchanging the inorganic sodium carbonate base for an organic base caused a dramatic change in the product distribution. The *Z-anti*-Markovnikov product (**117**) was predominantly obtained and produced with very high selectivity by altering the reaction conditions, and utilising DMAP and an alternative phosphine ligand (Scheme **3.4**).

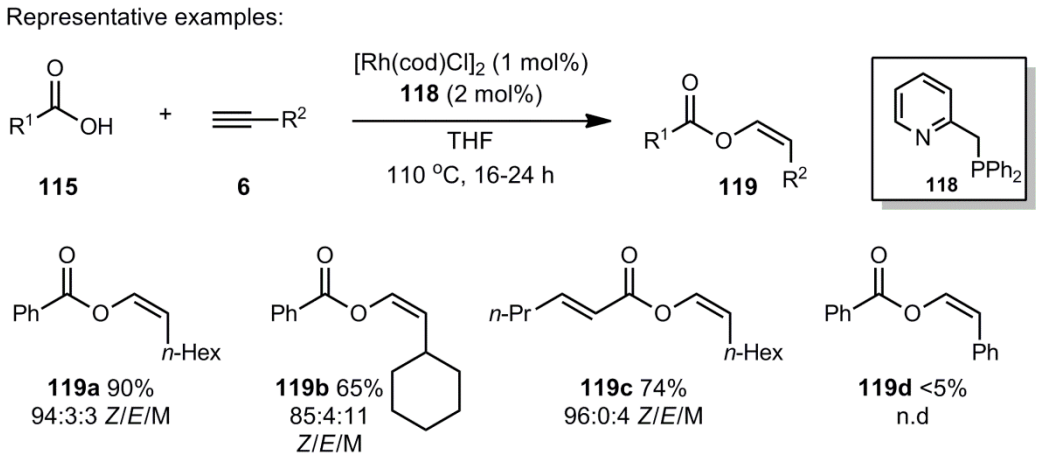


Scheme 3.4

In all examples reported, the desired enol ester was produced in a 50:1 isomeric ratio. Although the product selectivity was much more consistent than in the Markovnikov method (Scheme **3.3**), yields were unfortunately lower in some cases (**117d** *vs* **116d** and **117e** *vs* **116f**). These lower yields suggest that a bulky *t*-butyl substituted alkyne or the presence of a NH group are less compatible with the above catalytic system than that of Scheme **3.3**.

Although a full mechanistic discussion was not included by Gooβen and co-workers, the dramatic alteration in product selectivity was partly rationalised by the assumption that DMAP would coordinate to the ruthenium, thus providing a structurally different active catalyst to that of Scheme **3.3**. Thus, this catalyst would naturally operate through a different mechanism. The DMAP-based catalyst has similar product selectivity to related ruthenium catalyst-based systems with chelating ligands, which are known to be selective for *anti*-Markovnikov products.[68] Overall, the method of Gooβen and co-workers has provided a means to obtain either the Markovnikov or *Z-anti*-Markovnikov enol ester isomer in high selectivity, using practical reaction conditions. However, the substrate scope appears limited as only use of terminal alkynes was reported.

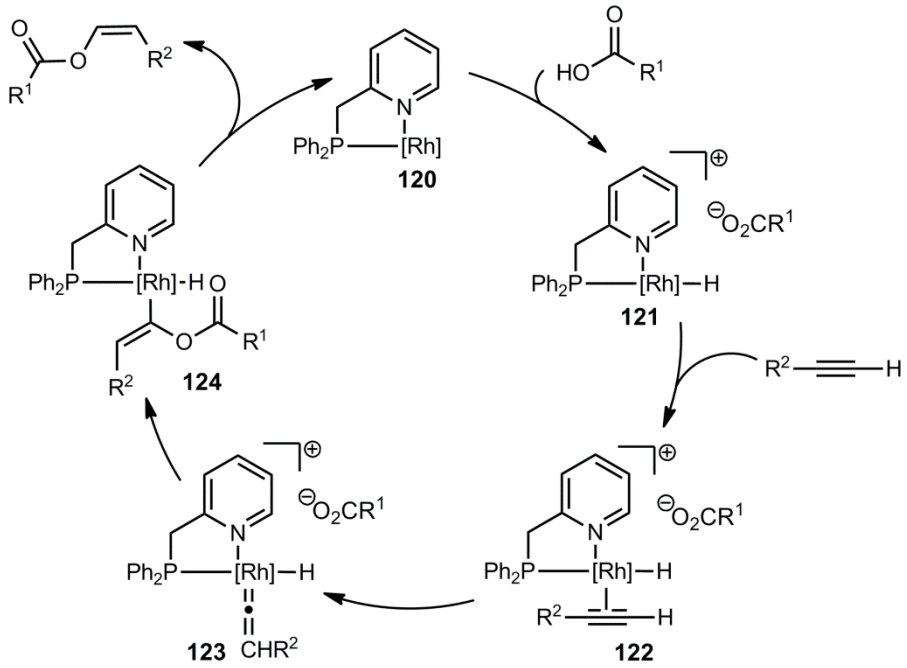
In a recent publication by Breit and co-workers, rhodium catalysis was used to selectively obtain *Z*-enol esters from terminal alkynes (Scheme **3.5**).[69] A ligand screen was carried out to obtain conditions that provided high product selectivity, and ligand **118** was found to be optimal. The selected ligand is very similar to the reagents used by Gooβen and co-workers (Scheme **3.4**), but in this case pyridine and phosphine components are both present on the same structure (**118**).



Scheme 3.5

Except for product **119d**, all of the enol esters reported were obtained in good to excellent yields (**119a-c**). In most cases, the isomeric ratio of the product was excellent (**119a**, **119c**). The ratios shown in Scheme **3.5** correspond to the ratio of the

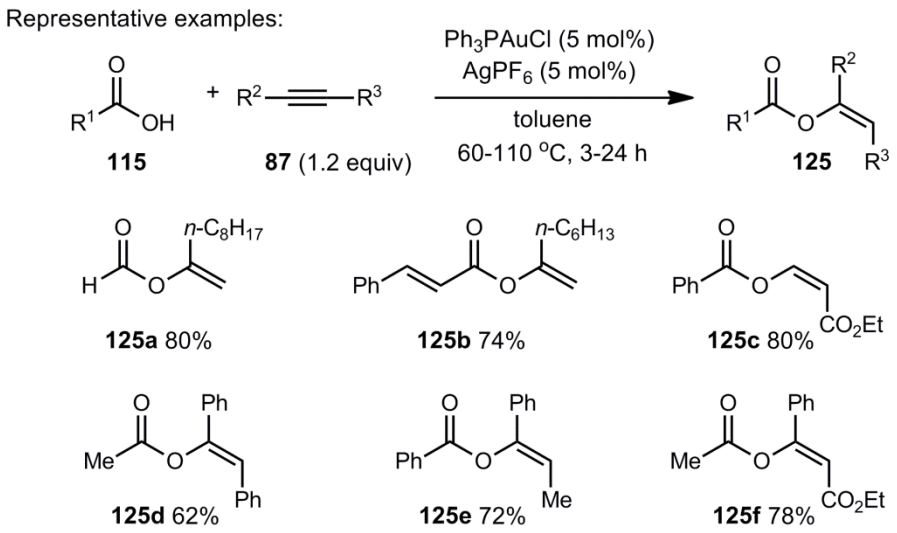
desired *Z*-enol ester to the corresponding *E*-enol ester and Markovnikov enol ester products respectively. The carboxylic acids used in this publication included aliphatic, aromatic, and heteroaromatic variants, as well as amino acids. The mechanism of the reaction was thought to involve a rhodium vinylidene intermediate (Scheme **3.6**), due to the terminal nature of the alkyne substrates.



Scheme 3.6 – Drawn as specified in the relevant publiation[69]

The proposed mechanism proceeds by oxidative addition of the carboxylic acid to the rhodium (**121**), followed by coordination of the alkyne and formation of vinylidene intermediate **123**. Addition of the acid to the most electrophilic carbon then occurs, generating **124**, and subsequent reductive elimination releases the enol ester product.

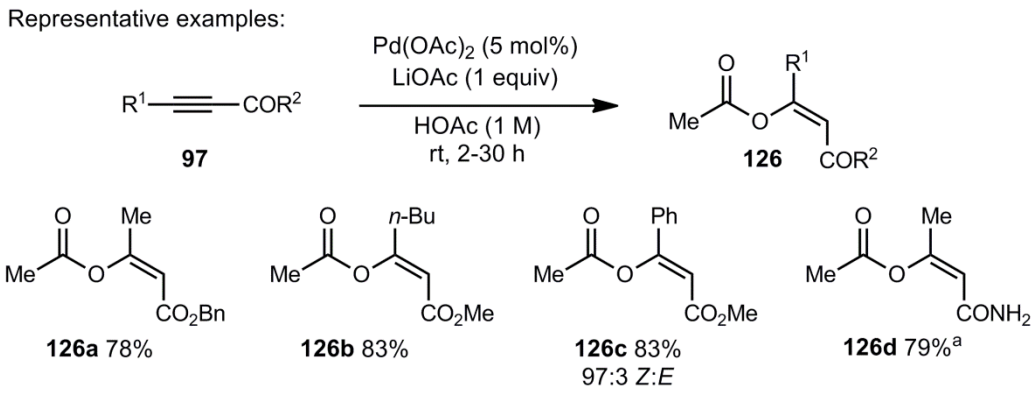
Gold catalysis can also be used for the hydroacyloxylation of alkynes, and a procedure developed by Chary and Kim was successful for the reaction of some internal alkynes, as well as terminal alkynes (Scheme **3.7**).[70]



Scheme 3.7

When terminal aliphatic alkynes were utilised, the Markovnikov products were selectively produced in good yield (**125a**-**b**). However, the use of an alkynoate caused addition of the acid to occur β to the ester group (**125c**), likely through a conjugate addition-type mechanism. Remarkably, with two unsymmetrical internal alkynes the products were successfully obtained as a single isomer and in good yield (**125e**, **125f**). A wide variety of carboxylic acids were used, including formic (**125a**) and trifluoroacetic acid. Overall, Chary and Kim have demonstrated a fairly broad substrate scope for their procedure, with a large range of carboxylic acids and a brief investigation of internal alkynes.

In 1992, palladium(II) acetate was employed by Lu and co-workers for the use of a certain subclass of internal alkynes in hydroacyloxylation (Scheme **3.8**).[71] This procedure largely utilised alkynoates and involved both lithium acetate and acetic acid, so it is unclear which acetate entity attacks the alkyne. The resulting *Z*-enol ester products (**126**) were formed stereo- and regio-specifically, in high yield and under mild conditions.



Scheme 3.8

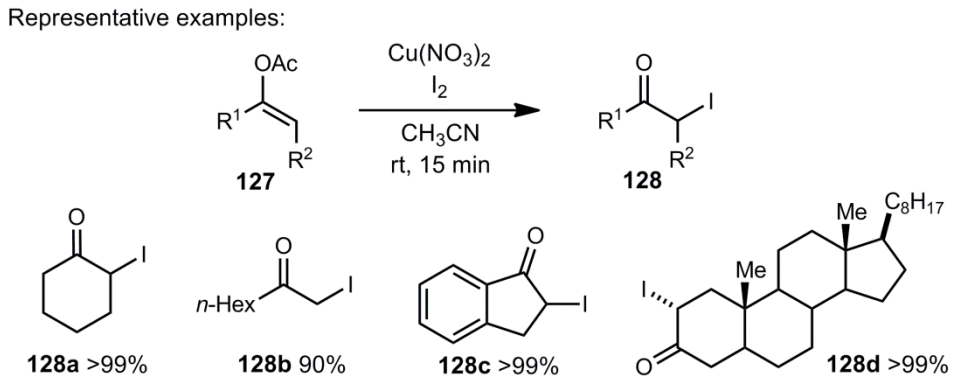
Acetate addition occurred at the more electrophilic carbon of the alkyne, β to the carbonyl group, resulting in a regioselective reaction (**126a-d**). It was found that altering the ester group on the alkyne did not significantly affect the yield (**126a** *vs* **126b**), but the process is only shown to be effective with acetic acid. An attempt at employing trifluoroacetic acid resulted in hydration of the alkyne to give a ketone, rather than providing the desired enol ester.

In conclusion, the examples shown indicate that carboxylic acid addition to alkynes occurs readily with various metal catalysts, but formation of a single product isomer requires careful control. Selective reactions of unsymmetrical internal alkynes are uncommon, and the formation of *E*-enol esters is relatively rare, regardless of the alkyne structure.

3.1.2 Reactions of Enol Esters

There are many known applications of enol esters, including polymerisation reactions,[72] cyclopropanation,[73] epoxidation,[74] enyne cyclisation,[75] and aldol-[76] and Mannich-type[77] reactions. Enol esters are a good replacement for *in situ* enolate formation from ketones, as they have a predefined, fixed enolate geometry and are much easier to handle.

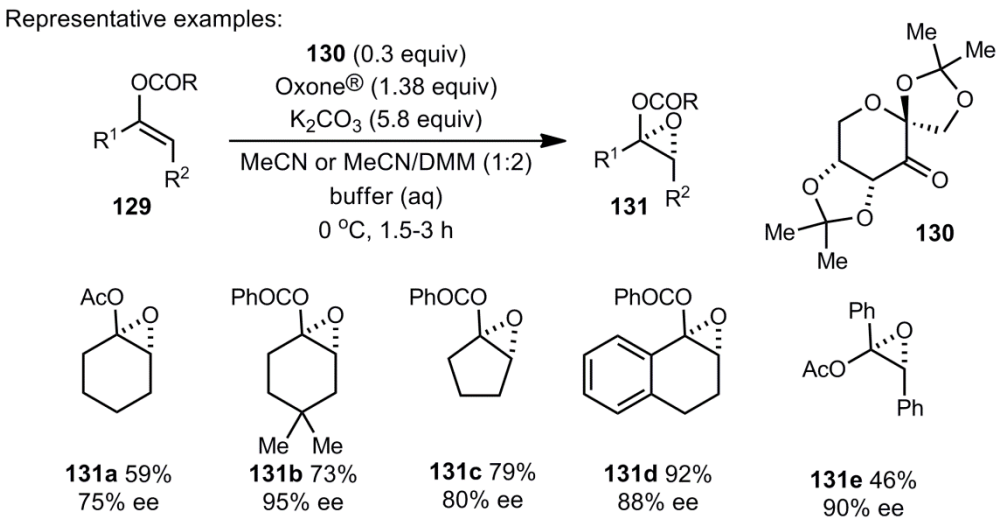
One more traditional use of enol esters is in the synthesis of α-iodo carbonyl compounds, as demonstrated in a publication by Cort in 1991.[78] The developed procedure (Scheme **3.9**) is stated to be more convenient and less toxic than previous routes to α-iodo carbonyl compounds, for example, in comparison to a method that utilises thallium acetate.[79]



Scheme 3.9

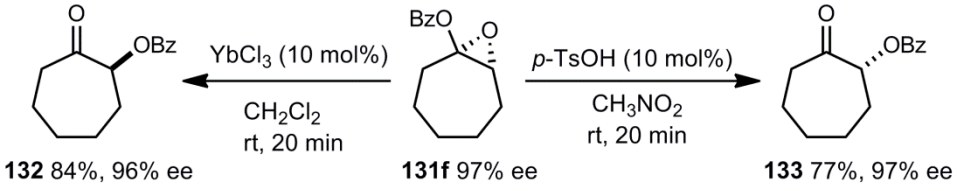
The use of enol acetates (**127**) in Cort's procedure resulted in very high yields of the α-iodo carbonyl compounds being obtained (**128a-d**). It was thought that copper(II) has a dual role in this reaction, as both a Lewis acid catalyst and a re-oxidant of iodide to iodine. It is possible that further improvements could be made to this method by development of catalytic copper conditions.

More recently, Shi and co-workers have developed a very effective asymmetric epoxidation of enol esters (Scheme **3.10**).[74] This method used fructose-derived ketone **130** as the chiral catalyst and Oxone® as the oxidant.



Scheme 3.10

Both cyclic and acyclic enol esters were suitable substrates for this methodology (**131a-e**). In general, the epoxidation of benzoate enol esters provided higher yields (**131b-d**) than acetate enol esters (**131a**). For cyclic enol ester substrates, different ring sizes were well tolerated, with examples incorporating five- to eight-membered rings being reported. Shi and co-workers then demonstrated that the epoxides readily rearrange to α-acyloxyketones (Scheme **3.11**). Different protic acid, Lewis acid and thermal conditions were investigated, and it emerged that both α-acyloxyketone enantiomers could be selectively produced (**132**, **133**), through careful choice of the reaction conditions.

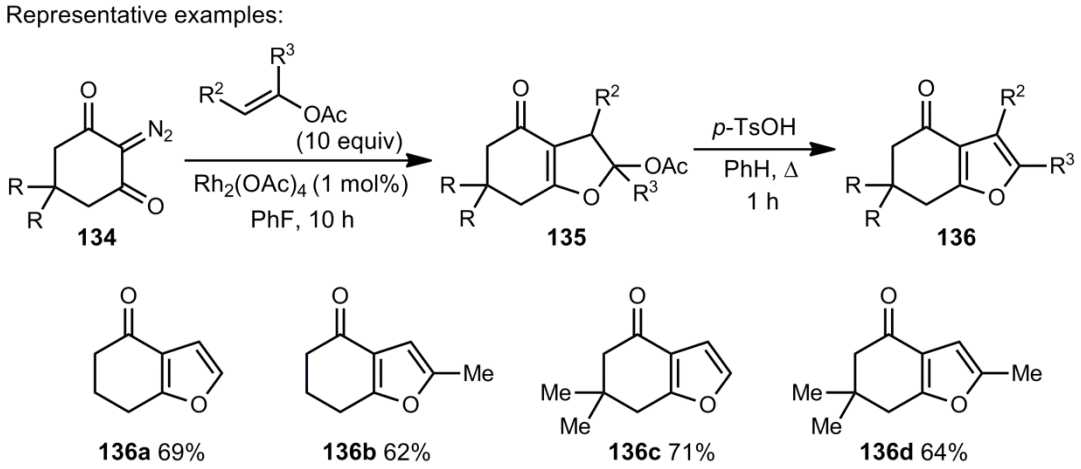


Scheme 3.11

The epoxidation conditions used by Shi and co-workers are complex, but overall the publication shows a worthwhile, asymmetric utilisation of enol esters.

Another notable example of enol ester chemistry is the rhodium-catalysed cycloaddition between enol esters and diazocyclohexane-1,3-diones (**134**), reported

by Pirrung and Lee in 1994.[80] The intermediates (**135**) produced from cycloaddition were subjected to acid-catalysed elimination of the acetate group, resulting in furan derivatives (**136**).



Scheme 3.12

This two-step process provides substituted furans in moderate to good yields (**136a-d**) and shows a very interesting use of enol esters. Furan **136a** was efficiently transformed into benzofuran natural products pongamol and lanceolatin B (Figure **3.1**), further illustrating the useful compounds that can synthesised through involvement of enol esters.

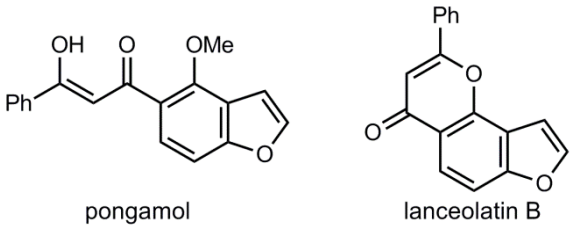
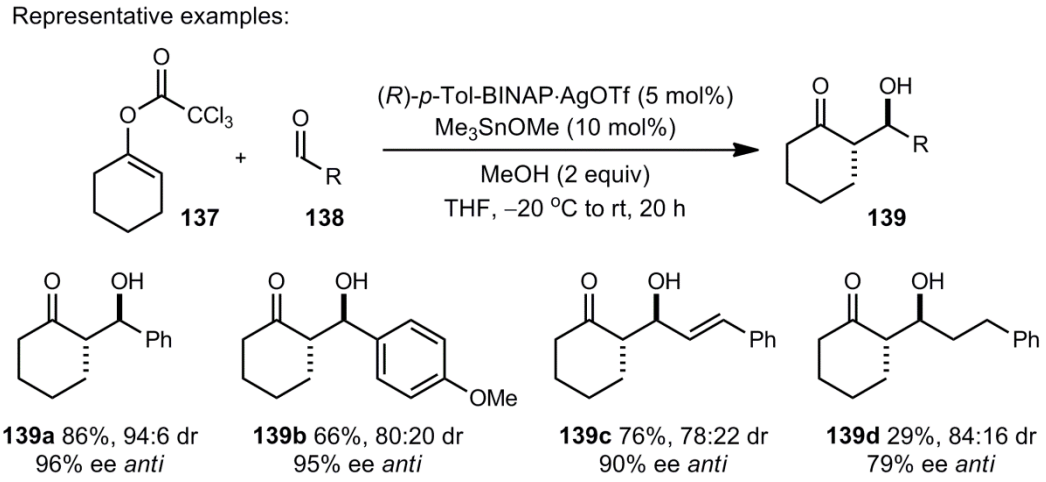


Figure 3.1

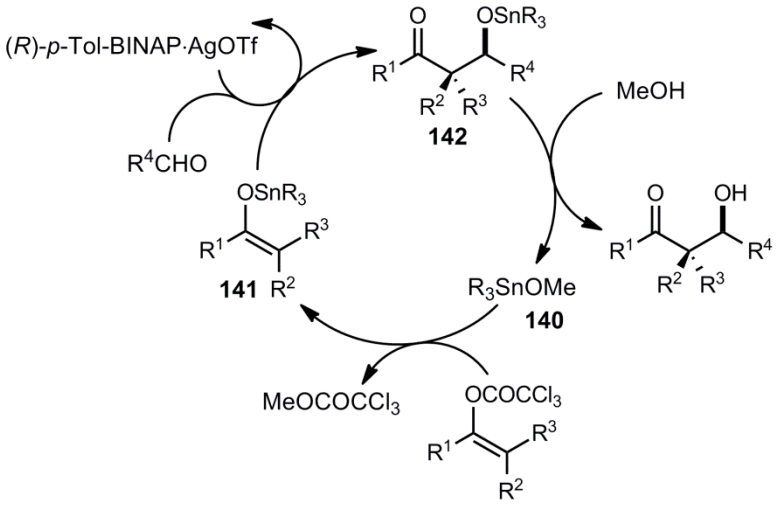
There are a number of publications that report the use of trichloroacetate enol esters in nucleophilic addition reactions, for example with aldehydes,[76c,81] aldimines[77a] or nitrosobenzene.[82] One publication by Yamamoto and co-workers[76c] described a tin methoxide mediated aldol reaction of trichloroacetate enol esters (Scheme **3.13**). The β-hydroxyketone products were predominantly of the *anti* configuration (**139**). A

catalytic silver-BINAP complex was also used, to provide enantioenriched products through asymmetric activation of the aldehyde.



Scheme 3.13

Optimisation of the reaction conditions produced **139a** in high diastereomeric ratio and enantioselectivity. Application of these conditions to other aldehydes was successful in some cases (**139b**, **139c**), but when aliphatic aldehydes were employed the reactivity was poor (for example **139d**). The mechanism proposed (Scheme **3.14**) shows the enol ester first being converted to a tin enolate (**141**), before undergoing a Lewis acid catalysed reaction with the aldehyde. The resultant tin adduct (**142**) is hydrolysed by methanol, to release the desired product. Evidence for this mechanism was provided through NMR studies.



Scheme 3.14 – Drawn as specified in the relevant publication[76c]

Yamamoto and co-workers also published a titanium catalysed version of this aldol reaction, where undesirable tin reagents were not required; however, the enantioselectivity of the reaction was generally lower by this method.[81]

As enol esters can undergo such a wide variety of transformations, it was hoped that α-acyloxyenamides would also be synthetically useful. Development of a method for synthesis of α-acyloxyenamides from ynamides would provide an opportunity to explore the chemistry of the resulting α-acyloxyenamide products.

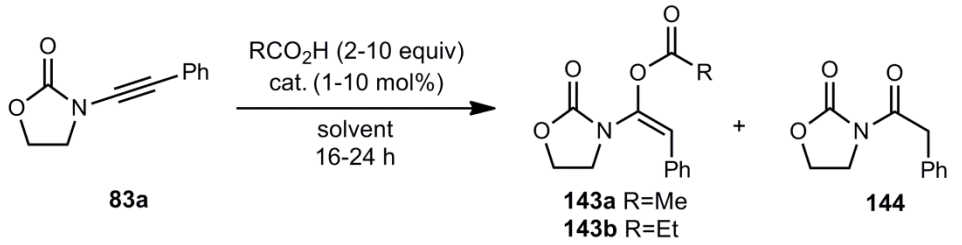
3.2 Results and Discussion[83]

3.2.1 Screening and Optimisation

Following an examination of the available literature regarding the addition of carboxylic acids to alkynes, a number of related metal pre-catalysts were screened for suitability in promoting the addition of carboxylic acids to ynamides. A selection of these screening experiments, for which either acetic or propionic acid were used, is shown in Table **3.1**. As well as requiring good conversion of the ynamide to occur, a high level of regio- and stereoselectivity, and a low proportion of imide **144** were needed. Imide **144**[84] was detected on a number of occasions when developing

conditions for the hydroacyloxylation of ynamides, and presumably, **144** is produced through *in situ* hydrolysis of the desired enol ester product (**143a**/**b**).

Table 3.1: Hydroacyloxylation Screening Reactions



83a **143a** R=Me **143b** R=Et **144**

Entry	R	Pre-catalyst	Additive	Solvent	Temp	143 (%)	144 (%)
1	Et	$RuCl_3 \cdot xH_2O$	-	toluene	70 ºC	23	-
2	Et	$[RuCl_2(p\text{-cymene})]_2$	$P(2\text{-Fur})_3$, Na_2CO_3	4:1 toluene/ THF	70 ºC	14	52
3	Et	$[RuCp^*(MeCN)_3]PF_6$	-	toluene	70 ºC	60	40
4	Me	$[Rh(cod)(MeCN)_2]BF_4$	-	THF	rt	43	3
5	Me	$Au(PPh_3)_3Cl$	AgOTf	CH_2Cl_2	rt	12	61
6[a]	Me	$Pd(OAc)_2$	-	toluene	90 ºC	87	9
7	Et	$Pd(OCOCF_3)_2$	-	THF	rt	65	5

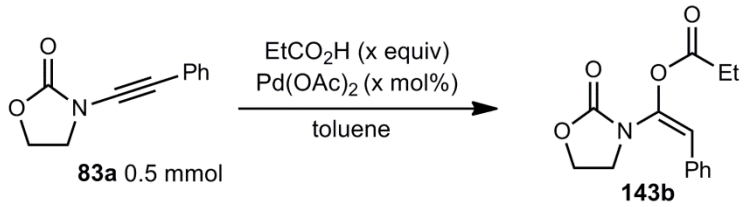
[a] Reaction conducted over 20 min, in a microwave reactor.

Ruthenium catalysis has been abundantly utilised in the past for alkyne hydroacyloxylation, but ruthenium proved unsatisfactory for the ynamide variant. Exposing ynamide **83a** to propionic acid at 70 °C, in the presence of $RuCl_3$ hydrate (7 mol%) provided only 23% conversion to **143b**. Conditions similar to that of Gooβen and co-workers[67] were also unsuccessful (entry 2), providing only 14% desired product (**143b**), along with significant imide (**144**) and isomeric enol ester side products. The use of a cationic ruthenium catalyst (entry 3) resulted in an initially promising conversion to **143b**, but a significant amount of imide **144** was also present. With the previously reported catalyst for ynamide carbometalation, $[Rh(cod)(MeCN)_2]BF_4$, mostly ynamide starting material remained with a moderate conversion to **143a** occurring (entry 4). Repetition of this experiment using microwave heating did not improve the conversion to desired product **143a**, only an increase in undesired side reactions was observed. A trial reaction using gold

catalysis (entry 5) resulted in a complex mixture of products, with imide **144** being the predominant component. Conducting the reaction in the presence of $Pd(OAc)_2$, at room temperature and in dichloromethane solvent, was unsuccessful, with only 20% conversion to the desired product and regioisomeric enol ester products evident. However, employing $Pd(OAc)_2$ under microwave reaction conditions (entry 6) resulted in a cleaner reaction and almost complete conversion to the desired product (**143a**). Given this success, use of $Pd(OCOCF_3)_2$ was attempted and a high consumption of the ynamide occurred, even at room temperature. Although desired product **143b** was the predominant component of the reaction mixture, unfortunately a significant amount of an isomeric enol ester product (5:1 ratio, in favour of **143b**) was also produced. In addition to the results in Table **3.1**, the use of $AuCl_3$ or $AgBF_4$ as the pre-catalyst was found to produce a complex product mixture, and employment of $Ni(acac)_2$, $Ni(PPh_3)_2Cl_2$, CuOAc, $Cu(OAc)_2$ or $Pd(PPh_3)_2Cl_2$ was found to give no or very little reaction of the ynamide. Overall, the results indicated that $Pd(OAc)_2$ was the most suitable catalyst for the proposed hydroacyloxylation of ynamides.

It was discovered that product **143a**, from addition of acetic acid to the ynamide, was not sufficiently stable for purification by chromatography on silica gel, as widespread hydrolysis to imide **144** occurred when purification was attempted. The product from propionic acid addition (**143b**) was found to be sufficiently stable, and this carboxylic acid was used for the majority of the optimisation studies. A brief solvent screen, using $Pd(OAc)_2$ and the reaction conditions detailed for entry 6 (Table **3.1**), found that use of dichloromethane or toluene resulted in a cleaner reaction than when using THF, and that acetonitrile was not a suitable solvent for the reaction. Due to the low boiling point of dichloromethane, toluene was selected for the remainder of the hydroacyloxylation reactions. With the chosen metal pre-catalyst and solvent in hand, optimisation of the reaction temperature and catalyst loading were carried out. The relevant experiments are shown in Table **3.2**.

Table 3.2: Reaction Optimisation



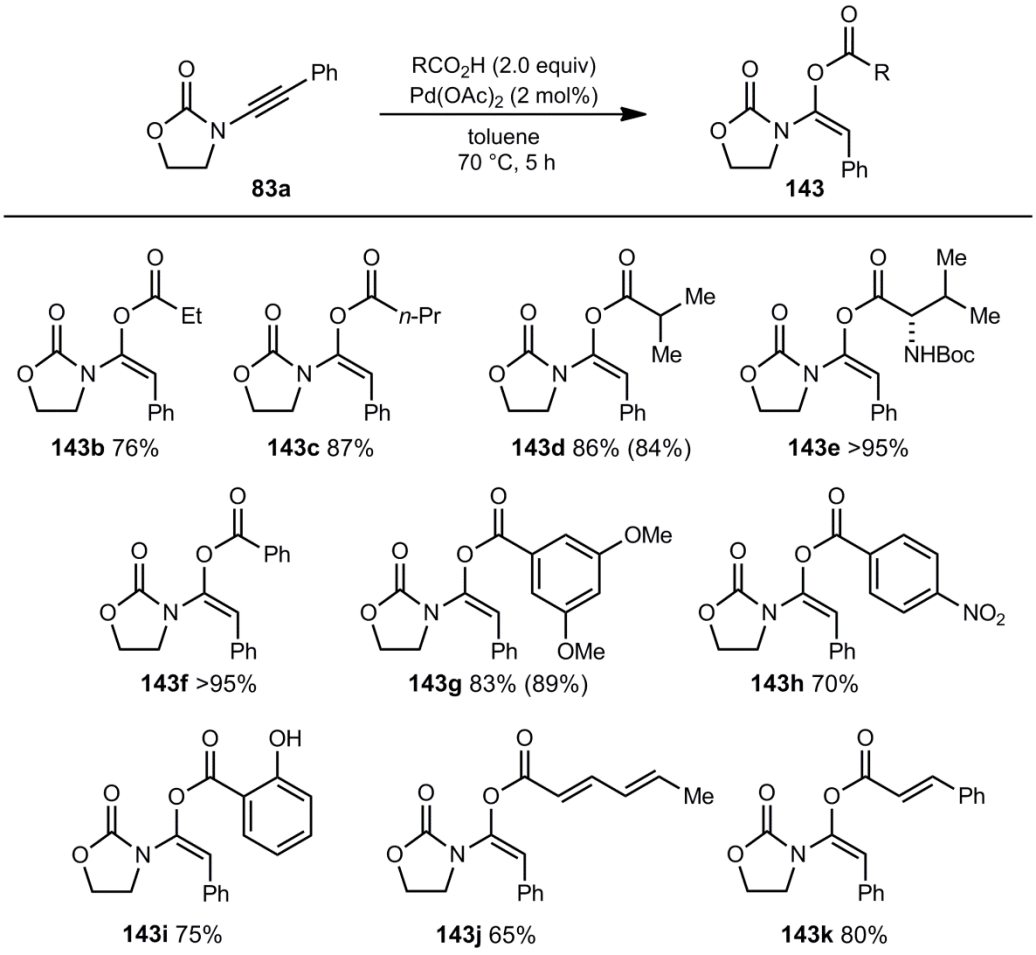
Entry	Acid Equiv	[Pd] (mol%)	Temp	Time	Yield (%)
1	5	2	90 ºC μW	1.5 h	70
2	5	2	70 ºC μW	2 h	80
3	2	5	70 ºC	5 h	63
4	2	2	70 ºC	5 h	76

Results showed that decreasing the reaction temperature (entry 1 *vs* entry 2) and the catalyst loading (entry 3 *vs* entry 4) increased the yield of **143b**, and that two equivalents of carboxylic acid was sufficient (entry 4). Use of a microwave reactor required long reaction times, so no benefit over conventional heating was apparent. Thus, the conditions in entry 4 were chosen as the optimal conditions for the hydroacyloxylation of ynamides. Pleasingly, the optimal conditions obtained are simple to use, and require no obscure catalysts, extra ligands or additional reagents.

3.2.2 Exploration of the Carboxylic Acid Scope

Under the optimised reaction conditions, ynamide **83a** was subjected to a wide range of carboxylic acids. It was found that many carboxylic acids can be successfully utilised (Table **3.3**) under the newly developed conditions and that the desired regio- and stereoselectivity was maintained throughout.

Table 3.3: Carboxylic Acid Scope[a]

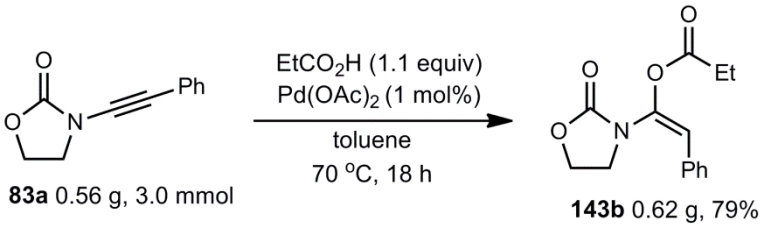


[a] Reactions were conducted on a 0.4 mmol scale. The yields in parenthesise refer to reactions conducted using 1.1 equiv of carboxylic acid.

All of the desired products (**143b-k**) were successfully isolated as a single isomer, in good to excellent yields. A high level of regio- and stereocontrol was evident in the ^{1}H NMR spectrum of the crude reaction mixture for each reaction. Although, the minor presence of **143a**, from addition of acetate from $Pd(OAc)_2$ to the ynamide, could be observed in the crude reaction mixture its effect on the yield is negligible. Both aliphatic and aromatic carboxylic acids were suitable reagents (**143c**, **143f**), and the reaction could even be conducted using an *N*-protected amino acid (**143e**). Interestingly, the use of an electron rich aryl group (**143g**) resulted in a higher yield than when an electron poor *p*-nitrophenyl group was utilised (**143h**). The presence of additional functionality was well tolerated in some cases, for example when including the phenol group of salicylic acid (**143i**) or an alkene (**143k**). However, a

slightly lower yield was obtained with sorbic acid, as product **143j** is more susceptible to hydrolysis than the other α-acyloxyenamides in Table **3.3**.

Throughout this chapter, selected experiments have been repeated using only 1.1 equivalents of the carboxylic acid (for example **143d** and **143g** in Table **3.3**). The results from all of these experiments were found to be comparable with the corresponding original result using two equivalents of acid, meaning that reduced quantities of more precious carboxylic acids can be used in this reaction. In addition, one hydroacyloxylation reaction was repeated on a preparative scale (Scheme **3.15**) to reinforce the utility and reproducibility of the reaction.

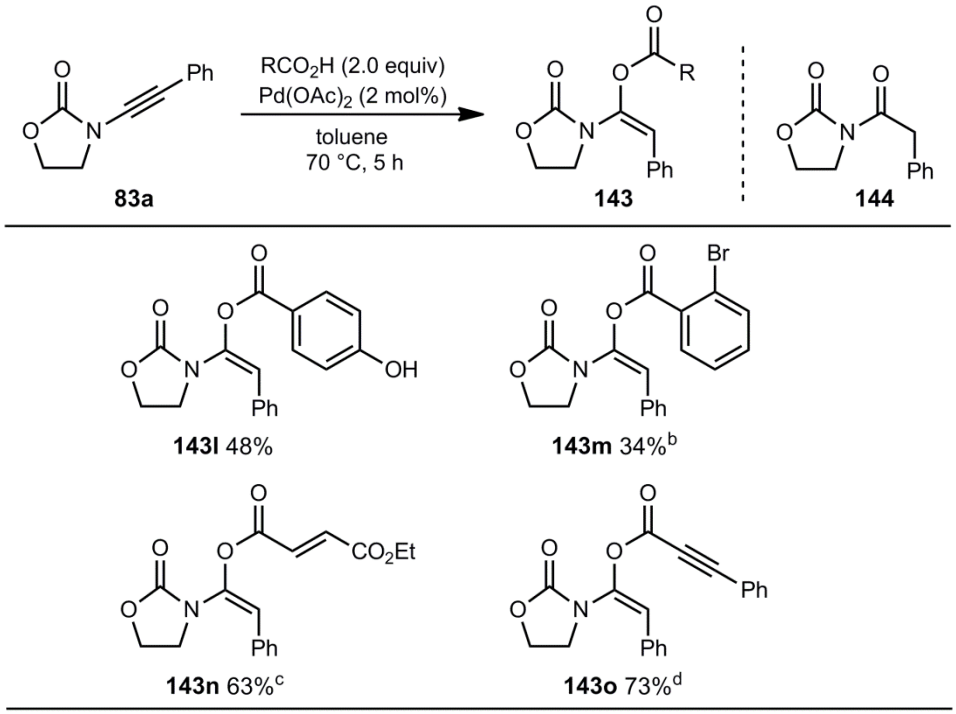


Scheme 3.15

Product **143b** was successfully obtained in a comparable yield to that obtained using the standard reaction conditions (**143b**, Table **3.3**), and this reaction also demonstrated that lowered catalyst loadings and carboxylic acid equivalents can still provide a high yield of the α-acyloxyenamide products.

During the exploration of the carboxylic acid scope, some of the hydroacyloxylation reactions encountered were more troublesome (Table **3.4**).

Table 3.4: Troublesome Carboxylic Acids[a]



[a] Reactions were conducted on 0.4 mmol scale. [b] A reaction time of 19 h was used. [c] Isolated as a 9:1 mixture of product and imide **144**. [d] 4.0 equiv of 3-phenylpropiolic acid and a reaction time of 24 h were used.

Reaction of ynamide **83a** with 4-hydroxybenzoic acid resulted in full consumption of the ynamide occurring but only a moderate yield of **143l**. Unknown side products were present in the reaction mixture, presumably as a consequence of the presence of the free hydroxyl group, thus the yield of **143l** was lower than expected. Similarly, when using 2-bromobenzoic acid minor side products were present in the crude reaction mixture and the isolated yield of α-acyloxyenamide **143m** was low. Initially, reaction of **83a** with mono-ethyl fumarate had appeared successful, through ^{1}H NMR analysis of the crude reaction product; however, α-acyloxyenamide **143n** was susceptible to hydrolysis during purification by column chromatography, and so the product was isolated as a 9:1 mixture of **143n** and imide **144**. The presence of additional alkyne functionality was then investigated by subjecting ynamide **83a** to 3-phenylpropiolic acid under the standard conditions. This reaction resulted in incomplete conversion of the ynamide and a low 31% yield of **143o**, due to de-carboxylation of the carboxylic acid occurring (the presence of phenylacetylene was observed)[85] and perhaps also due to 3-phenylpropiolic acid reacting with another molecule of itself, instead of the ynamide. Simply repeating the reaction with double

of the equivalents of the carboxylic acid resulted in a more successful reaction and provided **143o** in good yield.

Other carboxylic acids (**145a-e**) that were found to be unsuitable for producing α-acyloxyenamides are shown in Figure **3.2**.

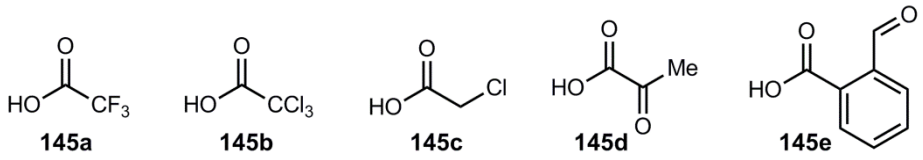


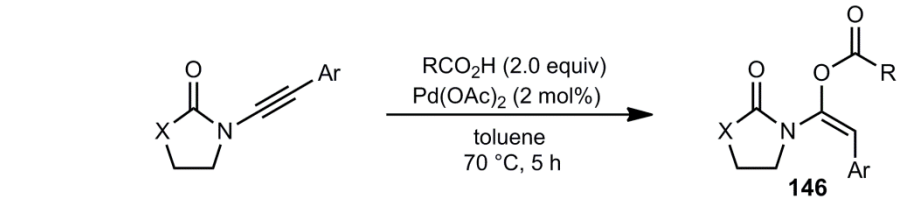
Figure 3.2

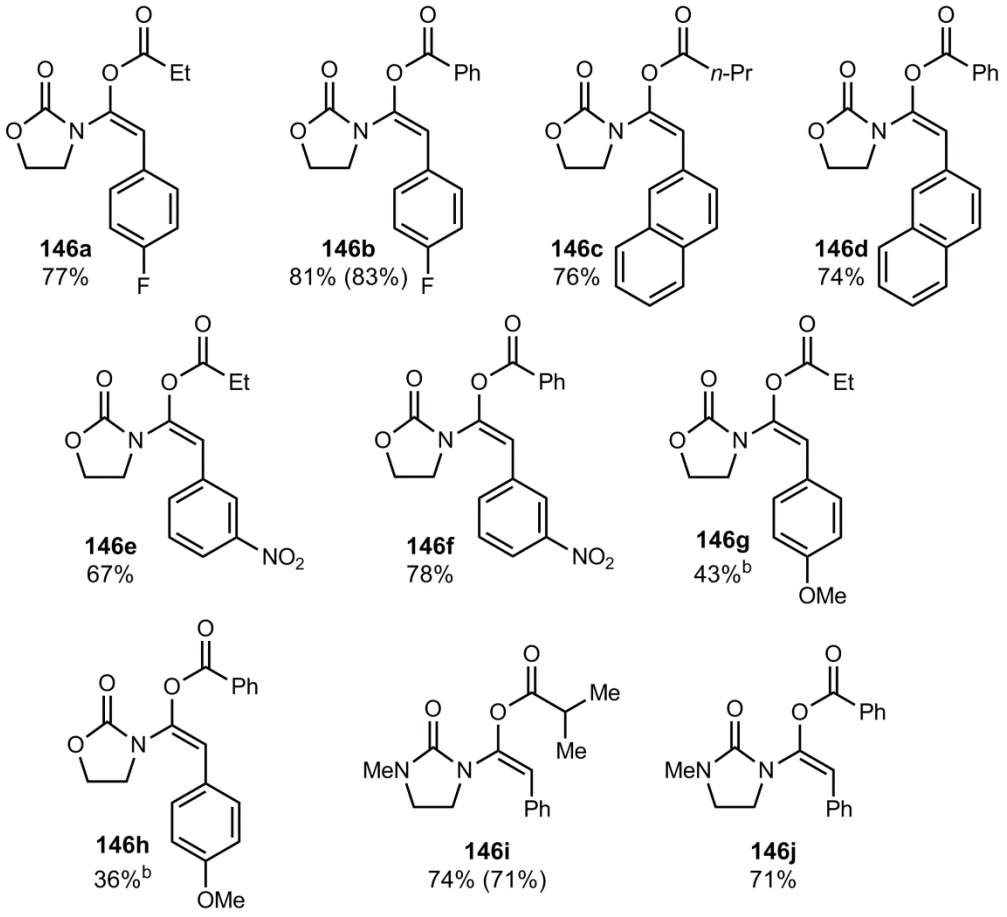
With all of the carboxylic acids in Figure **3.2**, significant amounts of imide side product **144** were formed during the course of reaction with ynamide **83a**, presumably because the expected α-acyloxyenamide products were too unstable to be obtained and instead underwent hydrolysis.

3.2.3 Hydroacyloxylation of Aryl-Substituted Ynamides

The ynamide scope of the developed method was explored by utilising some of the carboxylic acids that had been more successful in the hydroacyloxylation examples shown so far (Table **3.3**). The results of this investigation with different aryl-substituted ynamides are shown in Table **3.5**.

Table 3.5: Aryl-Substituted Ynamide Scope[a]



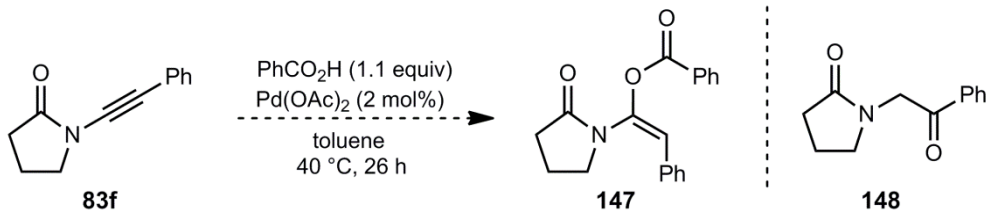


[a] Reactions were conducted on a 0.4 mmol scale. Yields in parenthesise refer to reactions using 1.1 equiv carboxylic acid. [b] 4 mol% $Pd(OAc)_2$ was used.

Ynamides substituted with a 2-naphthyl or 4-fluorophenyl group underwent the reaction successfully (**146a-d**), and a strongly electron-withdrawing nitro group could be included without hindering the reaction (**146e, 146f**). However, ynamide **83k**, containing an electron-rich 4-methoxyphenyl group, was found to be less reactive towards hydroacyloxylation. Increasing the catalyst loading resulted in apparent full consumption of the ynamide, but on isolation of the products the yields were low (**146g** and **146h**). Ynamides other than oxazolidinone-based ynamides could also be effective substrates, as employment of imidazolinone ynamide **83m**

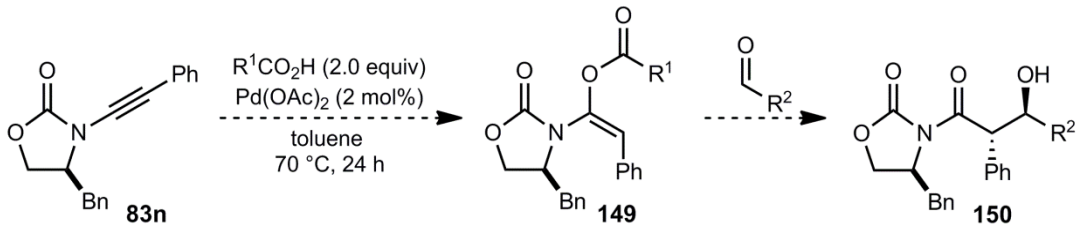
resulted in high yields (**146i, 146j**), despite a lower isomeric purity of the crude product being observed with this ynamide.

Pyrrolidinone-based ynamide **83f** was found to be an unsuitable substrate. When **83f** was subjected to the standard reaction conditions using benzoic acid, a complex mixture resulted. The ynamide appeared to have decomposed under the reaction conditions. A second reaction was conducted using milder conditions (Scheme **3.16**) to establish if conversion into **147** would improve. However, ketone **148**[86] was the only apparent product (20% conversion), accompanied by unreacted ynamide.



Scheme 3.16

It was hoped that ynamide **83n**, containing a chiral centre, would undergo hydroacyloxylation (Scheme **3.17**). The oxazolidinone group of **149** could then perform as a chiral auxiliary during further transformations, for example in an aldol-type reaction.

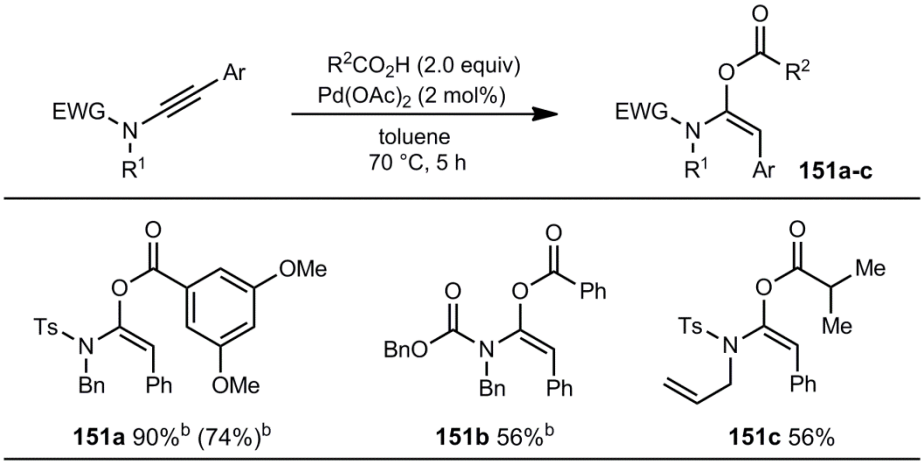


Scheme 3.17

However, ynamide **83n** unfortunately did not undergo the desired hydroacyloxylation reaction. Attempted reaction with *iso*-butyric acid resulted in no conversion of the ynamide occurring and a reaction with benzoic acid resulted in only 16% conversion to an undesired isomeric hydroacyloxylation product.

The ynamide scope was then explored further by investigation of aryl-substituted ynamides where the nitrogen atom is not part of a cyclic system. These types of ynamide have previously been unsuccessful substrates for methodology developed within the Lam group,[33,59] however, a number of these ynamides were found to be competent substrates for hydroacyloxylation (Table **3.6**).

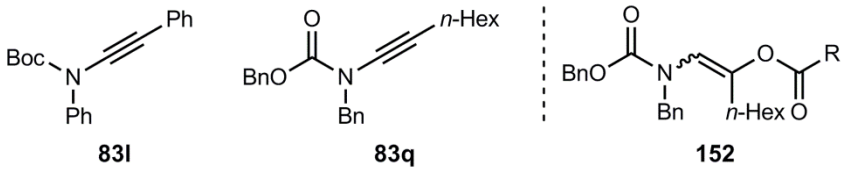
Table 3.6: Further Ynamide Hydroacyloxylation[a]



[a] Reactions were conducted on a 0.4 mmol scale. Yield in parenthesis refers to reaction using 1.1 equiv carboxylic acid. [b] A reaction time of 24 h was used.

Sulfonyl-based ynamide **83o** was a successful substrate and a very high yield of **151a** was obtained, once the standard reaction time had been extended. Ynamides **83g** and **83p** underwent the reaction, with complete consumption of the ynamide, but lower isolated yields were obtained (**151b**, **151c**). These moderate yields were due to competing side reactions occurring, the identity of which were unconfirmed.

Two further ynamides that were found to be unsuccessful substrates for hydroacyloxylation are shown in Figure **3.3**.



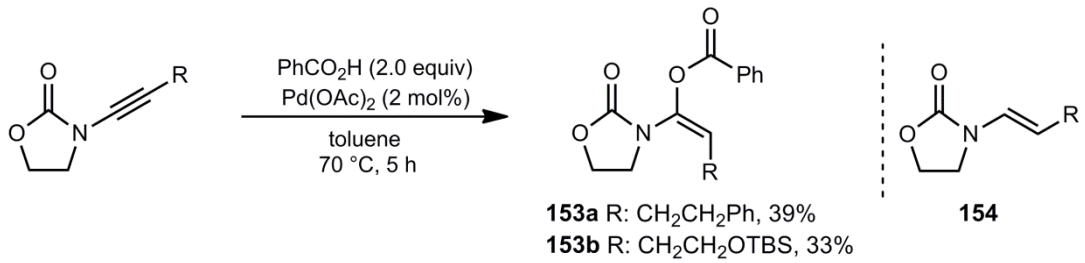
83l **83q** **152**

Figure 3.3

On treatment with propionic acid, ynamide **83l** underwent removal of the Boc group and hydroacyloxylation did not occur. Some hydroacyloxylation of ynamide **83q** occurred during reaction with either *iso*-butyric acid (54% conversion) or benzoic acid (42% conversion), but a regioisomeric β-acyloxyenamide product was produced in each case (**152**, stereochemistry unassigned), instead of the desired α-acyloxyenamide. These reactions had been performed on a small scale, and hence the regioisomeric products were not isolated.

3.2.4 Hydroacyloxylation of Aliphatic-Substituted Ynamides

The developed methodology was also applied to aliphatic-substituted oxazolidinone-based ynamides, with limited success. Initially, ynamides **83c** and **83b** were subjected to the standard reaction conditions (Scheme **3.18**). These conditions resulted in both full consumption of the ynamide occurring and a single isomer from hydroacyloxylation being observed. However, the isolated yields of the α-acyloxyenamides were low (**153a**, **153b**).

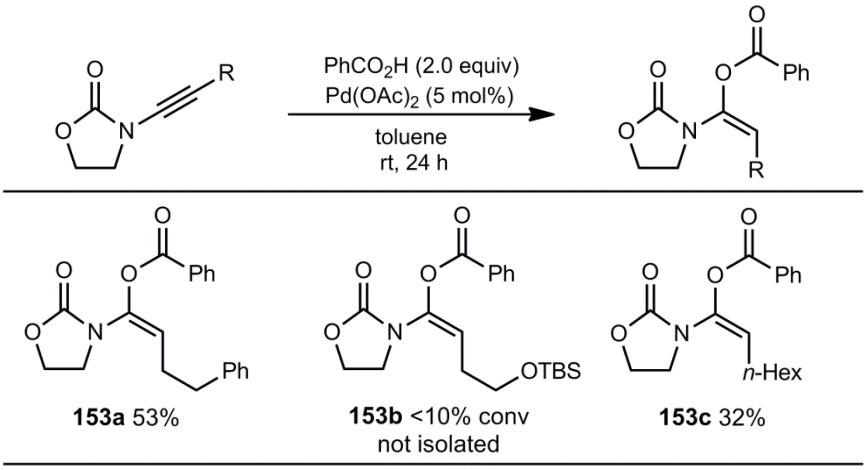


Scheme 3.18

The low yields were initially thought to be due to competing reduction of the ynamide triple bond under the reaction conditions, as minor signals tentively assigned to *E*-enamide **154** were present in the alkene region of the crude ^{1}H NMR spectra. However, no side products were isolated during chromatography. It was then proposed that the low yields could be due to decomposition of the product or ynamide occurring under the reaction conditions. Therefore, milder reaction conditions were used by conducting the reactions at room temperature (Table **3.7**).

The palladium catalyst loading was concurrently increased to ensure complete conversion of the ynamide still occurred.

Table 3.7: Hydroacyloxylation of Aliphatic Ynamides[a]



[a] Reactions were conducted on a 0.4 mmol scale.

Pleasingly, the yield of **153a** increased to 53% through lowering of the reaction temperature, but in the case of **153c**, the yield achieved was not greater than for the examples reported in Scheme **3.18**. On this occasion, a side product thought to be the stereoisomer of the desired α-acyloxyenamide was observed in the ^{1}H NMR spectrum of the crude reaction mixture for both **153a** and **153c** (in a 9:1 and 8:1 ratio respectively, in favour of **153**). For α-acyloxyenamide **153b**, the product was not isolated in this case as significant side products were present in the ^{1}H NMR spectrum of the crude reaction mixture; thus, the milder conditions were not beneficial for this example. In conclusion, the hydroacyloxylation of an aliphatic-substituted ynamide appears to require adjusting of the reaction conditions for each individual case, in order to maximise yields.

3.2.5 Regio- and Stereochemical Determinations

The structure of product **146f** was determined by X-ray crystallography (Figure **3.4**).

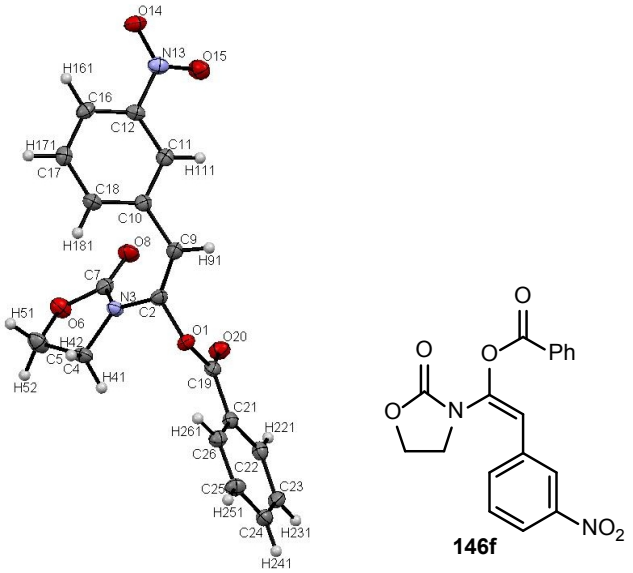


Figure 3.4[*]

The anticipated α-acyloxy-substituted enamide with *E*-geometry of the alkene was indeed obtained. The structures of the other hydroacyloxylation products were assigned by analogy.

NOESY experiments were also conducted on a number of the hydroacyloxylation products and the diagnostic interactions shown in Figure **3.5** were displayed.

[*] Christopher Cameron of The University of Edinburgh is acknowledged for X-ray crystallography.

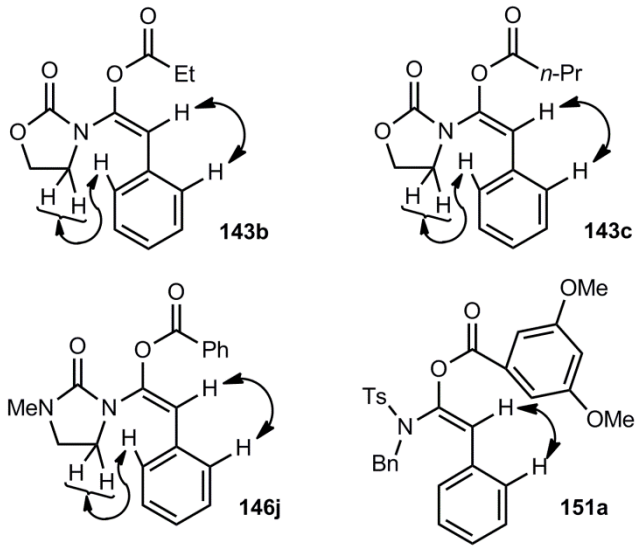


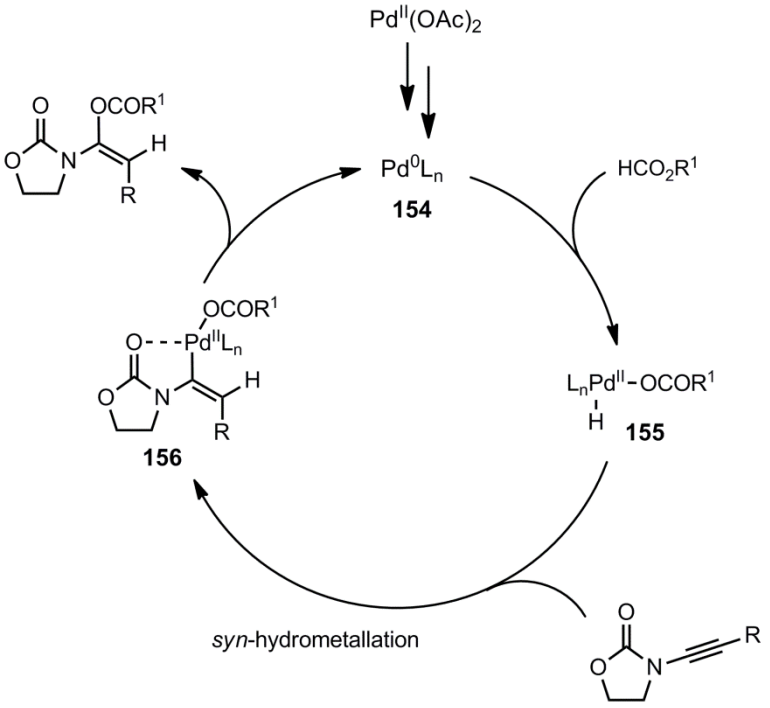
Figure 3.5

The diagnostic interactions in Figure **3.5** confirmed the regio- and stereochemistry of these examples to be consistent with that observed in the obtained crystal structure (Figure **3.4**). For compound **151a**, no interactions between the alkene proton and the tosyl, benzyl or methoxy groups were observed.

3.3 Mechanism

The mechanism of the palladium-catalysed hydroacyloxylation reaction remains unascertained. Two plausible mechanisms, that would indeed produce hydroacyloxylation products with the observed regio- and stereochemistry, are discussed in this section.

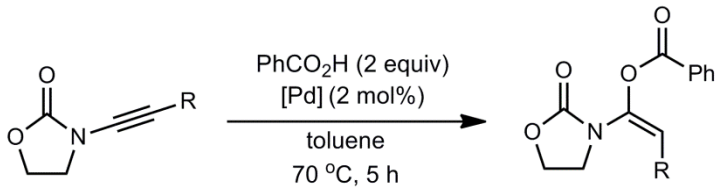
The first mechanistic option involves oxidative addition of the carboxylic acid to palladium (Scheme **3.19**).[87] For this mechanism to occur, presumably palladium(0) would first be formed *in situ* (**154**). Then oxidative addition of the carboxylic acid to palladium(0) can take place. The resulting palladium-hydride intermediate (**155**), would add to the ynamide in a *syn*-hydrometalation (**156**), with the carbonyl oxygen of the ynamide directing the palladium to the α-carbon. Finally, C-O reductive elimination would provide the hydroacyloxylation product and release palladium(0) to continue the catalytic cycle.



Scheme 3.19

If an oxidative addition mechanism is operating, then it would be expected that palladium(0) catalysts can also perform the desired hydroacyloxylation. Thus, in the hope of providing some mechanistic evidence, reactions using a palladium(0) source in place of palladium(II) acetate were conducted (Table **3.8**).

Table 3.8: Hydroacyloxylation Using Palladium(0)[a]

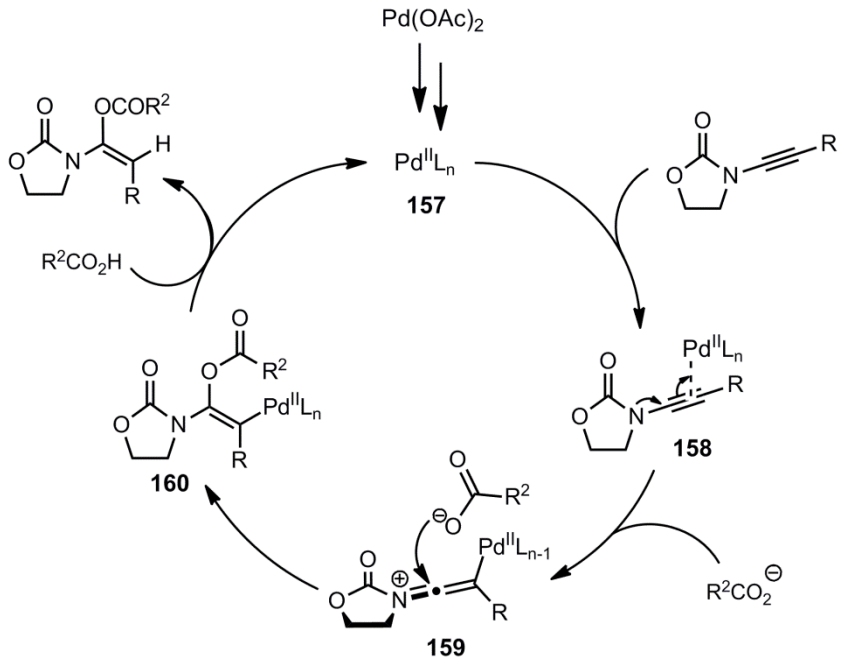


Entry	R	[Pd] (2 mol%)	Conv (%)	Yield
1	Ph	$Pd_2(dba)_3 \cdot dba$	>95	90%
2	*n*-Hex	$Pd_2(dba)_3 \cdot dba$	25	19%
3	Ph	$Pd(PPh_3)_4$	2	-
4	*n*-Hex	$Pd(PPh_3)_4$	6	-

[a] Reactions were conducted on a 0.2 mmol scale

As can be seen from the Table **3.8**, $Pd_2(dba)_3 \cdot dba$ was successful in mediating the hydroacyloxylation of ynamide **83a** under the standard reaction conditions, however, $Pd(PPh_3)_4$ was not successful (entry 1 *vs* 3). The failure of $Pd(PPh_3)_4$ to promote reaction of either ynamide **83a** or ynamide **83d**, could likely be due to an inability of $Pd(PPh_3)_4$ to form an active catalytic species under the specified conditions. The yield obtained from entry 2 is somewhat comparable to the use of $Pd(OAc)_2$, as only a low yield is obtained from the use of aliphatic ynamides under the standard conditions (see Scheme **3.18**). For entry 2, the reaction mixture also contained a side product tentatively assigned to be product **154** from ynamide reduction (in 20% conversion, see Scheme **3.18**). Ynamide reduction products were not apparent in the other reactions in Table **3.8**. It can be concluded from the results in Table **3.8** that hydroacyloxylation may operate *via* the proposed oxidative addition mechanistic cycle.

A second proposed mechanism involves palladium(II) catalysis and generation of a keteniminium ion intermediate[88] (Scheme **3.20**).



Scheme 3.20

The mechanism would occur through π-Lewis acid activation of the ynamide by palladium(II) (**158**), leading to palladation of the triple bond and keteniminium ion formation (**159**). Attack of a carboxylate species on to this keteniminium intermediate, from the same side as the palladium and perhaps *via* coordination to the palladium, would result in intermediate **160**. Protonation of intermediate **160**, under the acidic reaction conditions, then provides the hydroacyloxylation product and releases palladium(II).

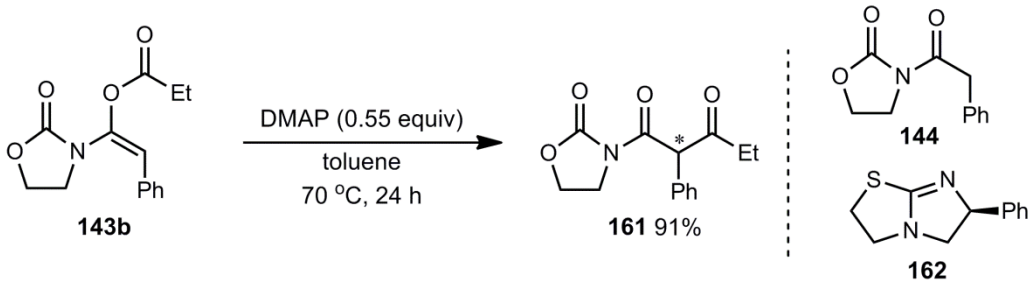
The mechanism depicted in Scheme **3.20** is consistent with the high regio- and stereoselectivity observed in the hydroacyloxylation reactions. Here, the regioselectivity is controlled through carboxylate addition to the most electrophilic carbon of the triple bond, and the stereoselectivity is controlled by *syn*-oxypalladation occurring. The fact that ynamides possessing a nitrogen atom and electron-withdrawing group that are not part of a cyclic system can be successful substrates for the developed hydroacyloxylation (see Table **3.6**), but not for the previously published carbometalation procedures,[33,59] suggests that the hydroacyloxylation reaction occurs through a mechanism that does not rely on coordination of a metal centre to the ynamide carbonyl oxygen. This provides some justification for the keteniminium-based mechanism (Scheme **3.20**) being the correct mechanism rather than the oxidative addition mechanism (Scheme **3.19**).

Both the oxidative addition mechanism (Scheme **3.19**) and the keteniminium-based mechanism (Scheme **3.20**) are plausible. In the absence of further evidence, neither mechanism can be definitively ruled out. It may also be possible that each hydroacyloxylation reaction is occurring by a slightly different mechanism, depending on the specific substrates used in each case.

3.4 Product Manipulations

In an attempt to show the synthetic utility of the hydroacyloxylation products, a preliminary investigation into the reactivity of α-acyloxyenamides was conducted.

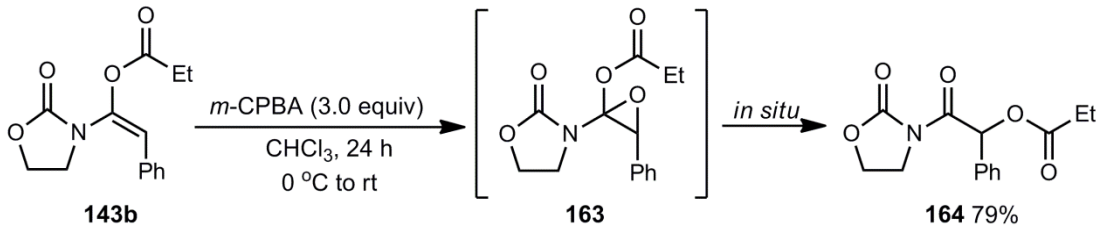
Firstly, an acyl transfer reaction was successfully achieved using substoichiometric quantities of DMAP,[89] generating a β-ketoimide (Scheme **3.21**).



Scheme 3.21

The desired product (**161**) was achieved in a high yield. Attempts at utilising a lower quantity of DMAP (20 mol%) unfortunately resulted in undesired imide **144** being present in the crude reaction mixture. It was thought that the reaction could be rendered enantioselective through the use of (-)-tetramisole (**162**) as the acyl transfer reagent,[90] but this was found to be unsuccessful as no reaction occurred when using this reagent. A more successful alternative for enantioselective transformation of **143b** into β-ketoimide **161** could perhaps be to use a chiral derivative of DMAP.[91]

Next, an α-propionoxyimide was produced by reaction of α-acyloxyenamide **143b** with *m*-CPBA (Scheme **3.22**).

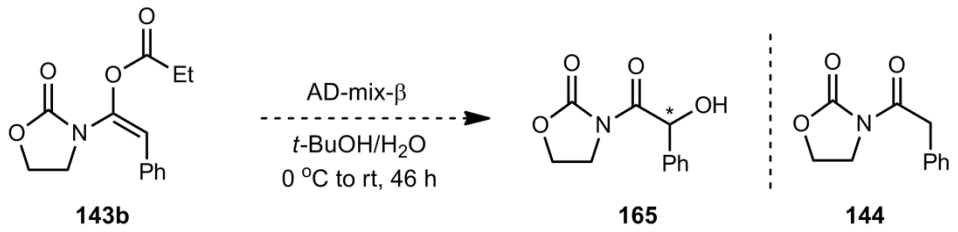


Scheme 3.22

Treatment with *m*-CPBA readily transformed the α-acyloxyenamide, but instead of the anticipated epoxide (**163**), compound **164** was obtained. It is assumed that the α-propionoxyimide was produced by an *in situ* rearrangement of an unstable intermediate epoxide. This transformation illustrates how the α-acyloxyenamides can

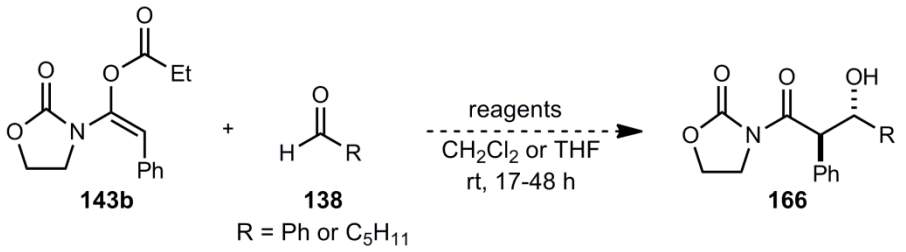
be further utilised without destroying any of the carefully installed functional groups, and in this case the alkene functionality was targeted. Again, an asymmetric version of the reaction could potentially be developed, providing enantioenriched **164**. This transformation could be accomplished using a chiral catalyt and an oxidant, perhaps employing Shi's conditions (Scheme **3.10**)[74] or Jacobsen's catalyst.[92]

Previously, the dihydroxylation of enamides had been reported by the Lam group,[43b] using the conditions in Scheme **3.23**. However, an attempted dihydroxylation of α-acyloxyenamide **143b** was unsuccessful. The reaction conditions used resulted in imide **144** predominantly being produced, instead of the desired product (**165**).



Scheme 3.23

It was then intended that the α-acyloxyenamides would participate in aldol-type reactions. Due to the *E*-geometry of the α-acyloxyenamides, undergoing reaction with an aldehyde should result in a fairly elusive *anti*-product being produced (according to the Zimmerman-Traxler model)[93]. If an aldol reaction was successful it could then potentially be performed enantioselectively, adding even further value to the transformation. To begin with, a variety of achiral reagents were investigated for facilitation of the aldol reaction (Scheme **3.24**).

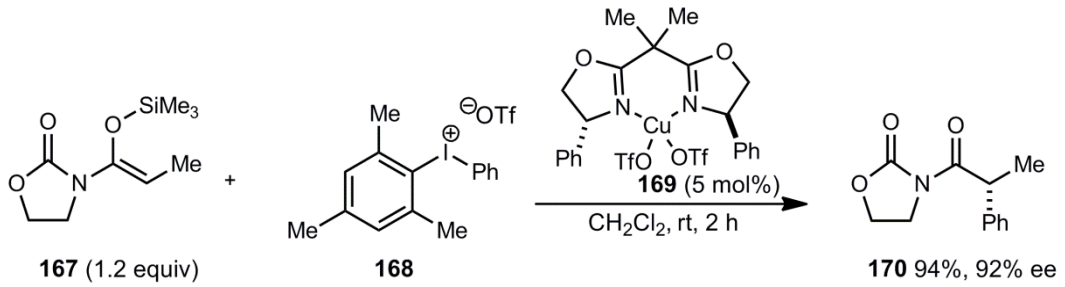


Reagents: $SnBu_3(OMe)$ (10 mol%) and MeOH (2 equiv), $Cu(OTf)_2$ (20 mol%), $TiCl_4$, $Ti(i\text{-}OPr)_4$, TMSOTf, or NaOMe

Scheme 3.24

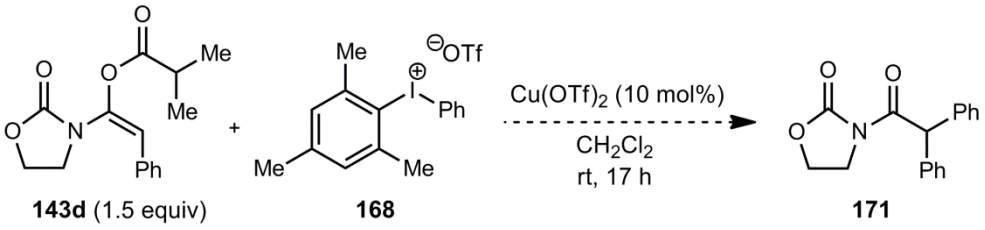
Unfortunately, no aldol reaction occurred under any of the conditions investigated. Even attempted replication of Yamamoto and co-workers' aldol procedure[76c] produced no desired result. In many cases hydrolysis to the corresponding imide (**144**) was apparent, indicating that cleavage of the enol ester was occurring but subsequent addition to the aldehyde was not. It became clear that either harsh conditions or stoichiometric reagents were potentially required for this aldol transformation and so developing a metal-catalysed enantioselective version of the reaction would be difficult. Thus, the investigation into an aldol-type reaction was not continued.

Gaunt and co-workers have published a procedure for the enantioselective arylation of silyl derivatives of *N*-acyloxazolidinones (**167**), using copper-box catalyst **169**.[94] Diaryliodonium salts (**168**) were used as the arylating reagent, and they react by transferring an aryl group from the iodine atom to the copper centre.



Scheme 3.25

It was anticipated, due to the similarities in structure between **167** and the α-acyloxyenamides, that the ynamide hydroacyloxylation products could also react under the arylation conditions. Consequently, α-acyloxyenamide (**143d**) was subjected to conditions similar to the racemic reaction conditions reported in the publication of Gaunt and co-workers (Scheme **3.26**).



Scheme 3.26

Unfortunately, in this case no reaction occurred and only starting material was recovered. The substrates used by Gaunt and co-workers had *Z*-geometry of the double bond (**167**), so the above reaction would have provided a complimentary way to access the arylated products. Perhaps with optimisation of the conditions, or careful preparation of Gaunt's copper-box catalyst (**169**), the desired reaction (Scheme **3.26**) could take place.

3.5 Conclusions

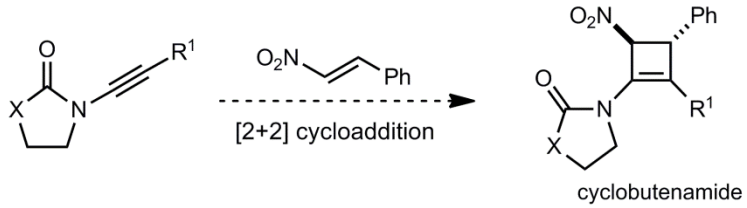
The successful development of a high-yielding method for the addition of carboxylic acids to ynamides has been achieved. This hydroacyloxylation process produced oxygen-substituted enamides, in the form of α-acyloxyenamides, in a highly regio- and stereocontrolled manner. A large range of products were produced, as a variety of carboxylic acids and ynamides were tolerated under the reaction conditions. The ynamide scope for the hydroacyloxylation reaction is much greater than the scope reported in most literature publications on the reaction of ynamides.

Moreover, the α-acyloxyenamide products produced have the potential to be useful in a variety of reactions, as an enol ester derivative. Some examples have been discussed, including an O- to C-acyl transfer reaction and reaction with *m*-CPBA.

Future work in the area of hydroacyloxylation of ynamides could include further investigations into the mechanism of addition of carboxylic acids to ynamides when using palladium(II) acetate. Additionally, more in depth investigations into the reactivity of α-acyloxyenamides could provide useful new reactions and enantioenriched compounds to the synthetic chemistry community.

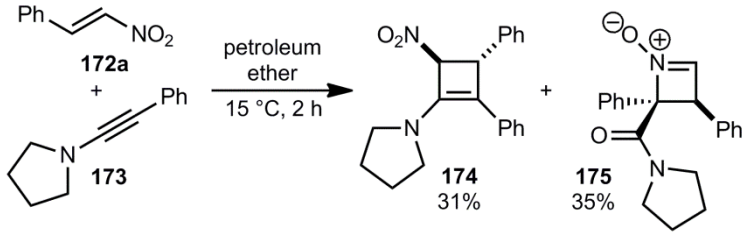
4. Rhodium-Catalysed [2+2] Cycloaddition of Ynamides with Nitroalkenes

Ynamides are known to undergo a variety of cycloaddition reactions.[1b] However, the [2+2] cycloaddition of ynamides with alkene moieties has been little explored. The [2+2] cycloaddition reaction of an ynamide with a nitroalkene had not previously been reported, and it was proposed to develop this reaction (Scheme **4.1)**.



Scheme 4.1

The closest precedent to the proposed [2+2] cycloaddition reaction is work by Reinhoudt and co-workers[95] describing the reaction of ynamines with nitroalkenes (Scheme **4.2**).[95a] This procedure is a version of the Ficini reaction,[96] the stepwise [2+2] cycloaddition of ynamines with electron-deficient alkenes to form cyclobutenamines.



Scheme 4.2

The reported reactions were shown to proceed without catalysis and to generate either cyclobutenamines (**174**), four-membered cyclic nitrones (**175**), or a mixture of both, depending on the substrate used. This difficulty in controlling the product distribution may be a result of the reactive nature of ynamines. Developing an improved protocol using ynamides would be advantageous, in that better control of

the product distribution to provide only cyclobutenamides in good yield should be possible and the use of reactive, difficult to handle ynamine substrates would be eliminated.

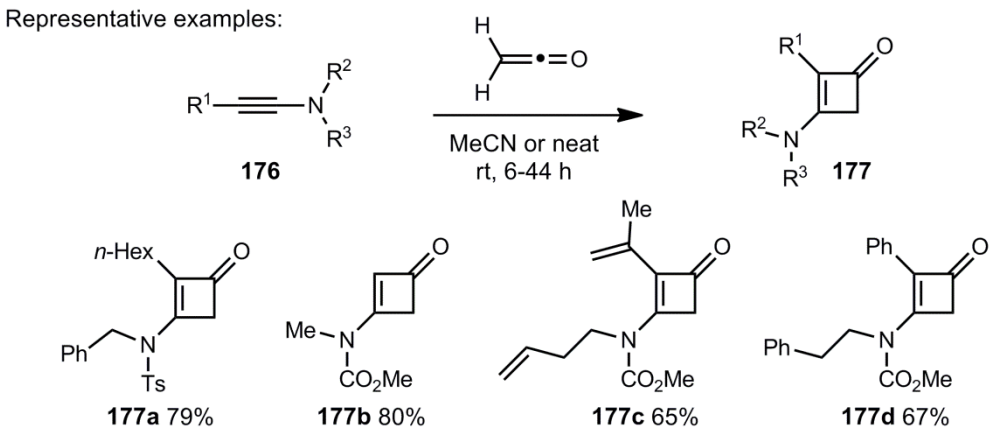
The development of a rhodium-catalysed [2+2] cycloaddition of ynamides with nitroalkenes, including optimisation of the reaction conditions and investigation into the scope and limitations of the cycloaddition reaction, will be discussed in the following chapter.

4.1 Introduction

Many cycloaddition reactions of ynamides have been reported, however, [2+2] cycloadditions with electron-deficient alkene coupling partners are uncommon. Other types of cycloaddition reactions using ynamides have proven very useful,[1b] for example, a [2+2+2] cycloaddition reaction that generates a number of fused rings in just one step[97] or utilisation of a [3+2] cycloaddition of ynamides in new methods to β-lactams.[98] Examples in the literature of [2+2] cycloadditions of ynamides include reactions with ketenes,[99] carbonyl compounds,[100] and imines,[101] but in terms of alkene coupling partners only strained bicyclic alkenes[60b,102] and more recently, cyclic enones[103] have been reported.

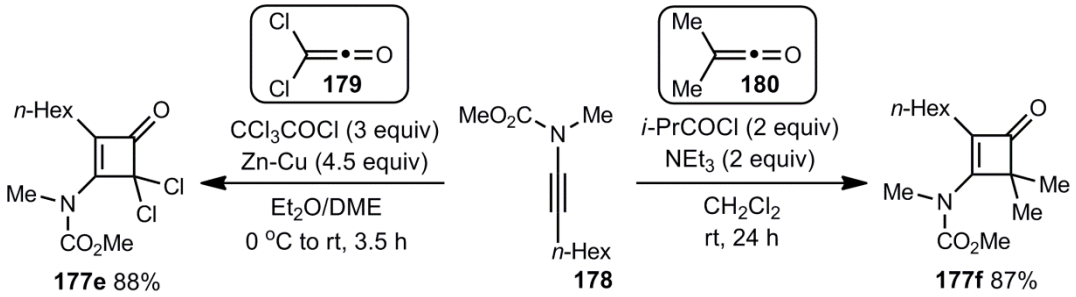
4.1.1 [2+2] Cycloaddition Reactions of Ynamides

Danheiser and co-workers published an efficient [2+2] cycloaddition of ynamides with ethenone (Scheme **4.3**).[99a] This uncatalysed reaction proceeded at room temperature to provide various cyclobutenones (**177**).



Scheme 4.3

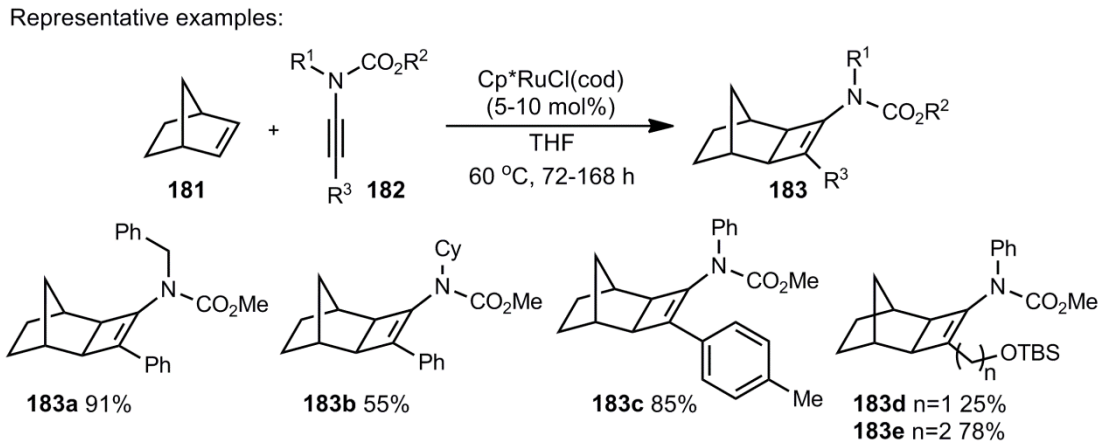
Ethenone was generated through pyrolysis of acetone and subsequently bubbled into the reaction mixture over five hours. A variety of ynamides, including a terminal ynamide and an ynamide containing an alkene moiety, were successful in the reaction (**177a-d**). In the case of **177c**, no undesired reaction of the ketene with the alkene was observed. In some cases, the reaction was found to proceed more rapidly in the absence of solvent. Other ketene derivatives were found to react well with ynamide **178**. These ketenes were generated *in situ* from the reagents listed in Scheme **4.4**.



Scheme 4.4

Dichloroketene (**179**) was generated by reductive dechlorination of trichloroacetyl chloride, and dimethylketene (**180**) was generated by base promoted dehydrohalogenation of isobutyryl chloride. High yields of the desired cyclobutenones were achieved (**177e**, **177f**). Overall, this method is effective in producing cyclobutenone products, but production of ethenone requires specialised equipment.

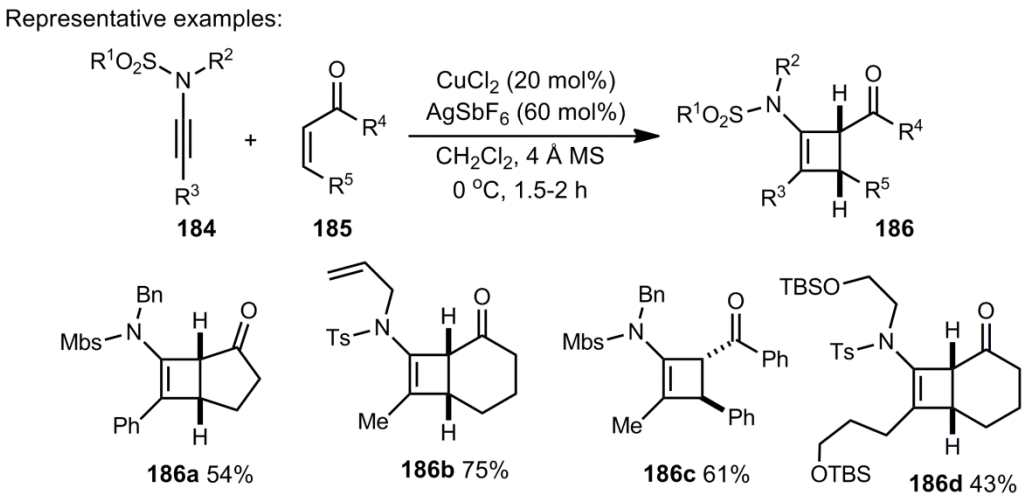
Tam and co-workers have developed a [2+2] cycloaddition of ynamides with the strained bicyclic alkene norbornene (**181**).[60b] This procedure uses ruthenium catalysis and generates cyclobutenamide products (**183**). Tam and co-workers found that ynamides undergo cycloaddition less readily than electron-deficient alkynes, but heating at 60 °C and using long reaction times afforded the desired products.



Scheme 4.5

For the different ynamides used in this study, only the *exo* diastereomers of the [2+2] cycloaddition products were observed and the yields reported ranged from moderate (for example **183b**) to excellent (**183a**). Interestingly, example **183d**, where the aliphatic substituent contains only one carbon atom, resulted in a poor yield and polymeric materials being observed, but lengthening to a two carbon chain resulted in a high yield (**183e**). No desired reaction occurred with terminal ynamide substrates; only undesired polymeric products were detected. The procedure was then extended to include a small number of other bicyclic alkenes and chiral ynamides.[102]

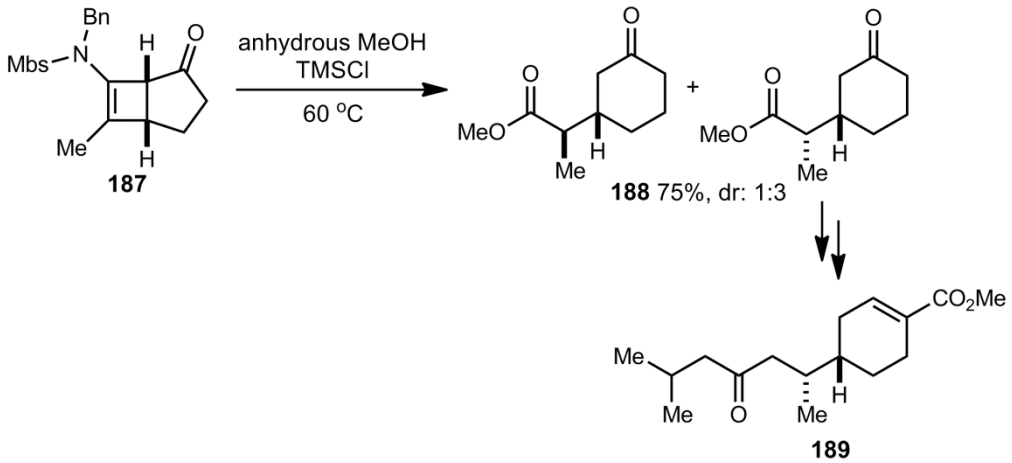
Hsung and co-workers described the first successful [2+2] cycloaddition of ynamides with enones in 2010 (Scheme **4.6**).[103a] This reaction is copper-catalysed and utilises ynesulfonamides (**184**), due to their increased nucleophilicity in comparison to amide- or urethane-substituted alkynes. It was stated by the authors that the use of oxazolidinone-based ynamides for cycloaddition attempts resulted in numerous failed experiments.



Scheme 4.6

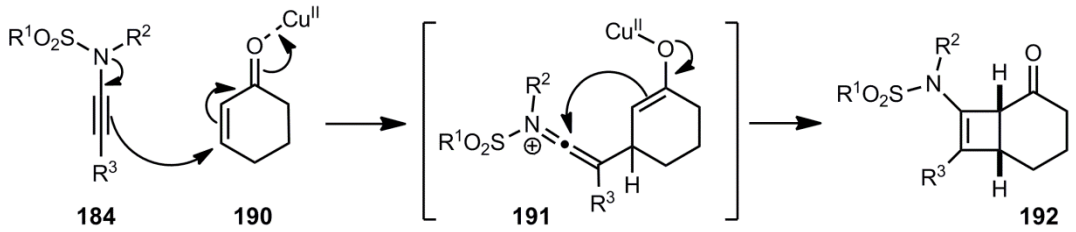
Good to moderate yields were obtained for the resulting cyclobutenamides (**186a-d**), with the highest reported yield being obtained for **186b**. Varying the identity of the sulfonyl group does not appear to have much effect on the yield, and it was found that terminal ynamides were unsuitable substrates for cycloaddition. Cyclohexenone was employed for the majority of the reactions, but cyclopentenone and two acylic ketones were also found to be efficient coupling partners (see **185a** and **185c**).

Hsung and co-workers then demonstrated that one of the cyclobutenamide products (**187**) could be hydrolysed to a keto-ester (**188**, Scheme **4.7**). The predominant *syn* diastereomer of this keto-ester is a known precursor of (±)-juvabione (**189**).[104]



Scheme 4.7

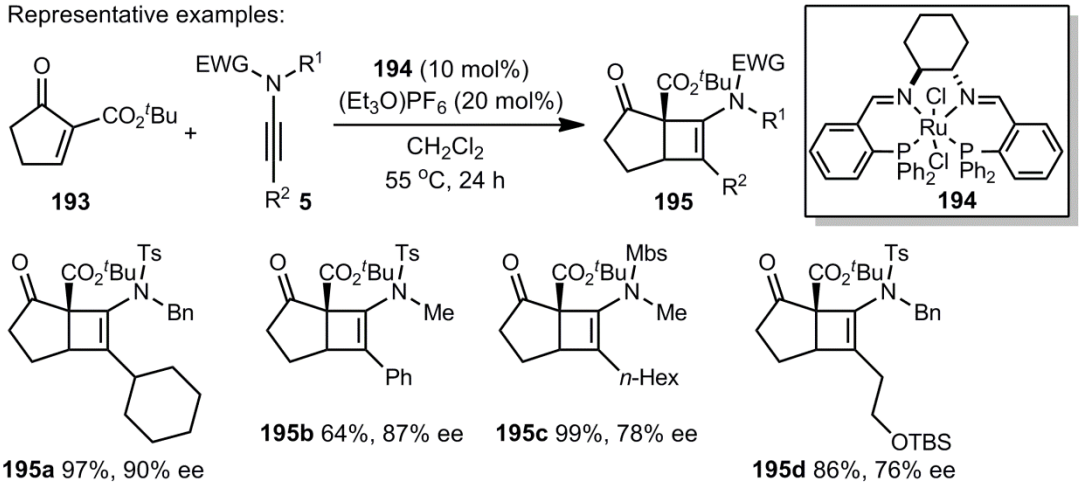
One plausible mechanism proposed by the authors consists of a step-wise pathway where cationic copper(II) activates the enone to 1,4-addition by the ynamide (Scheme **4.8**). This mechanism is similar to that originally proposed by Ficini.[96]



Scheme 4.8

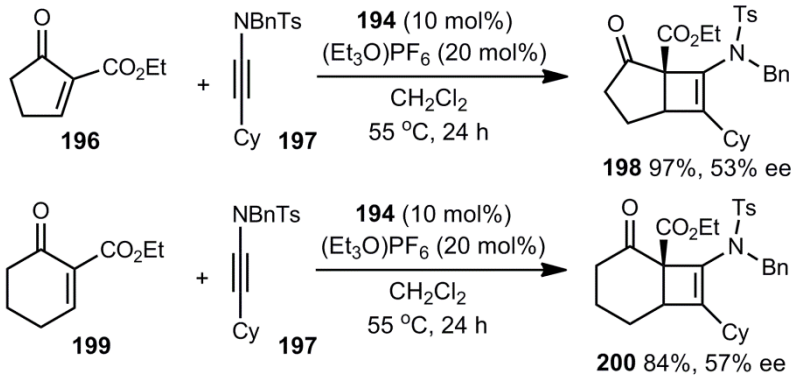
Overall, this publication provides interesting insight into the relative reactivity of different ynamides in [2+2] cycloaddition reactions, and highlights a potential application of cyclobutenamides in total synthesis.

Mezzetti and co-workers reported an enantioselective ruthenium-catalysed variant of Hsung and co-workers' procedure, using cyclic unsaturated β-ketoesters (**193**).[103b] The optimal substrates for Mezzetti and co-workers' reaction are ynamides that possess both an electron-withdrawing and electron-donating substituent on the nitrogen atom. This ensures that the ynamide undergoes the catalysed reaction efficiently but that the uncatalysed racemic background reaction does not occur, as the ynamide is not reactive enough.



Scheme 4.9

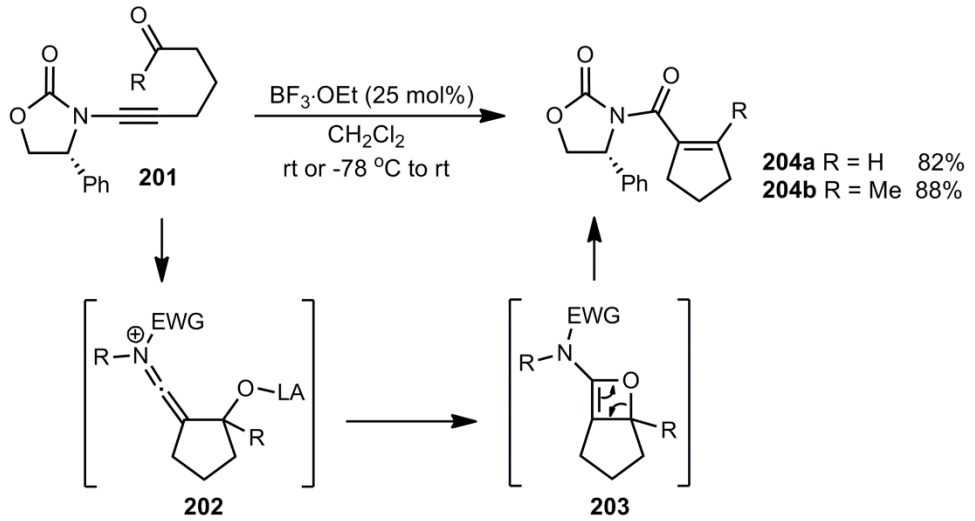
A number of excellent yields were reported in this publication (for example **195a**, **195c**), irrespective of the sulfonyl group used. An enantiomeric excess greater than 70% was obtained for all examples involving enone **193**. The highest enantioselectivities were achieved when a bulky alkyne substituent, such as phenyl or cyclohexyl, was employed (**195a**, **195b**). Recrystallisation of **195a** produced a single enantiomer of the product in 75% yield. Alternative enones (**196**, **199**) possessing a sterically smaller ester substituent resulted in lowered enantioselectivity (Scheme **4.10**); however, the yields remained high (**198**, **200**), so it may be possible to achieve high enantioselectivity across a wide range of substrates with further catalyst development.



Scheme 4.10

This initial example of an enantioselective Ficini reaction with ynamides is a worthwhile process, although the substrate scope is limited to ynesulfonamides and unsaturated β-ketoesters in this publication.

Other reported reactions that involve ynamides participating in [2+2] cycloaddition reactions provide products that result from electrocyclic ring-opening of the original cycloaddition product.[100,101,105] In these cases, the intermediate cycloadduct is presumably not sufficiently stable to be isolated. An example of such a reaction is presented in a publication by Hsung and co-workers.[100b] Here, ynamides containing a tethered carbonyl group (for example **201**) undergo a Lewis acid-catalysed intramolecular formal [2 + 2] cycloaddition, followed by a ring-opening (Scheme **4.11**).



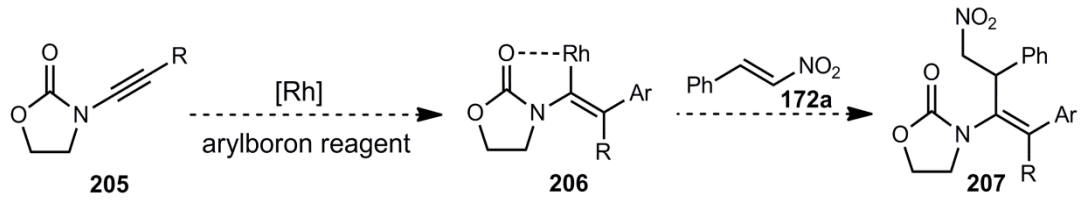
Scheme 4.11

The reaction is believed to proceed through cycloadduct oxetene **203** as shown in Scheme **4.11**. For this procedure, oxazolidinone ynamides (such as **201**) provided higher yields than ynesulfonamides, and five to seven-membered carbo- and heterocycles were able to be obtained as the reaction products.

After consideration of the relevant literature, it was concluded that pursuing the development of a [2+2] cycloaddition reaction between ynamides and nitroalkenes would be worthwhile. All previous [2+2] cycloaddition reactions of ynamides appear to have limited substrate scope, with the use of oxazolidinone-based ynamides being fairly elusive, and there is a tendency for *cis* cycloadducts or ring-opened products to be obtained, whereas the proposed [2+2] cycloaddition of ynamides was expected to result in *trans* cyclobutenamides as the major product. In addition, it may be possible to conduct the [2+2] cycloaddition reaction enantioselectively, further increasing the benefits of the process.

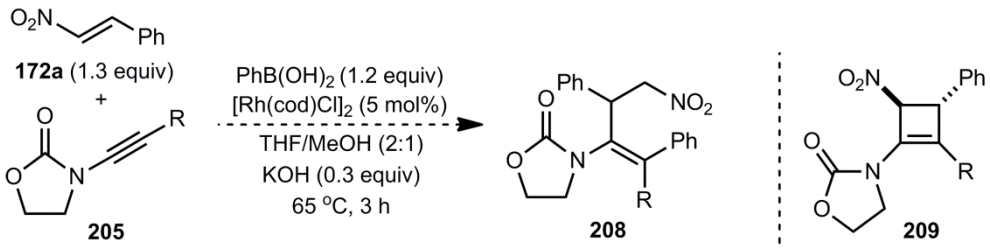
4.2 Results and Discussion[*,106]

The investigation into the [2+2] cycloaddition reaction of ynamides with nitroalkenes was initiated through an unexpected discovery. During an attempt at a rhodium catalysed sequential addition reaction involving ynamides, an unexpected [2+2] cycloaddition product was encountered. The initially proposed domino reaction sequence (Scheme **4.12**) consisted of ynamide arylation using an organoboron reagent (**206**), and then conjugate addition of the resulting alkenylrhodium intermediate to an electron-deficient alkene, such as *trans*-β-nitrostyrene (**172a**).



Scheme 4.12

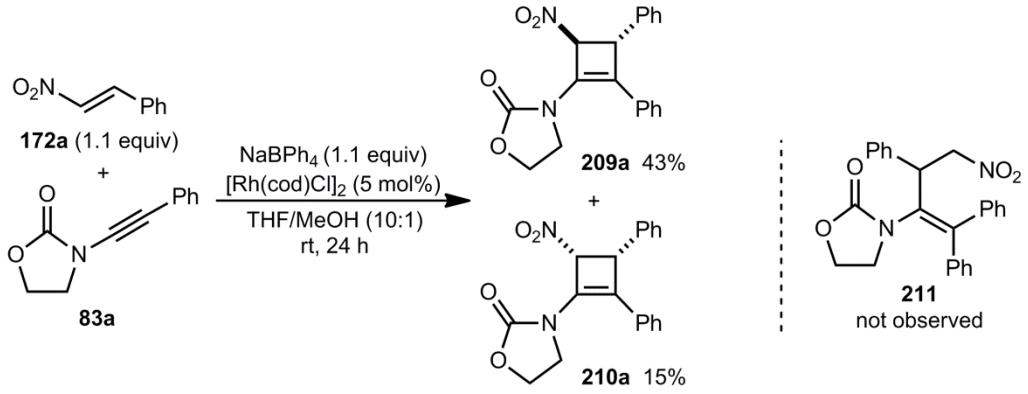
The proposed sequential addition reaction was attempted by Suresh Reddy Chidipudi with a number of oxazolidinone-based ynamides (Scheme **4.13**). Conditions similar to a previously published method by our group for the rhodium-catalysed annulation of ynamides[107] were used, however, instead of the anticipated product from sequential addition (**208**), product **209** resulting from [2+2] cycloaddition of the ynamide with *trans*-β-nitrostyrene was observed as a significant reaction product.



Scheme 4.13[†]

[*] This [2+2] cycloaddition project was initiated by Lam group member Suresh Reddy Chidipudi. Many of the initial ideas and discoveries were the work of Suresh Reddy Chidipudi.
[†] This reaction was conducted by Suresh Reddy Chidipudi.

It became apparent that in the presence of potassium hydroxide and methanol, some competitive decomposition of the nitroalkene was occurring. The replacement of potassium hydroxide and phenylboronic acid with sodium tetraphenylborate was thus investigated. Utilisation of sodium tetraphenylborate in a reaction of ynamide **83a** with *trans*-β-nitrostyrene (**172a**) again resulted in the initially unexpected cycloaddition product being produced (Scheme **4.14**).



Scheme 4.14

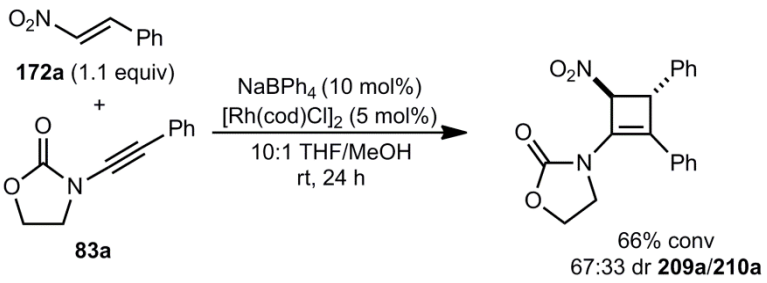
This reaction resulted in full consumption of the ynamide occurring and produced two diastereomers of the cycloaddition product in a 72:28 *trans* to *cis* ratio (determined by ^{1}H NMR analysis of the unpurified reaction mixtures). Pleasingly, the two diastereomers could be separated during column chromatography, which resulted in the isolated yields of **209a** and **210a** above.

4.2.1 Reaction Optimisation

It was established through control experiments that the presence of both a metal catalyst and an organoboron reagent was crucial for the [2+2] cycloaddition reaction to occur. In order to optimise the yield of the reaction, screening of many metal pre-catalysts and reaction conditions was carried out in collaboration with Suresh Reddy Chidipudi. It was found that only $[Rh(cod)Cl]_2$ or $[Rh(C_2H_4)Cl]_2$ in combination with a diene ligand provided the desired cycloaddition products. Various bis-phosphines were found to be unsuitable ligands for rhodium in the proposed [2+2] cycloaddition reaction. Lewis acid catalysts $Sn(OTf)_2$, $InBr_3$ and $CuCl_2/AgSbF_6$ showed an

inability to promote the [2+2] cycloaddition reaction, providing evidence that the reaction does not occur by a simple Lewis acid-catalysed process.[103]

Although the organoboron source is crucial for the reaction to occur, it was discovered that the organoboron reagent can be added in only catalytic amounts without drastically reducing conversion to the [2+2] cycloaddition product (Scheme **4.15**).

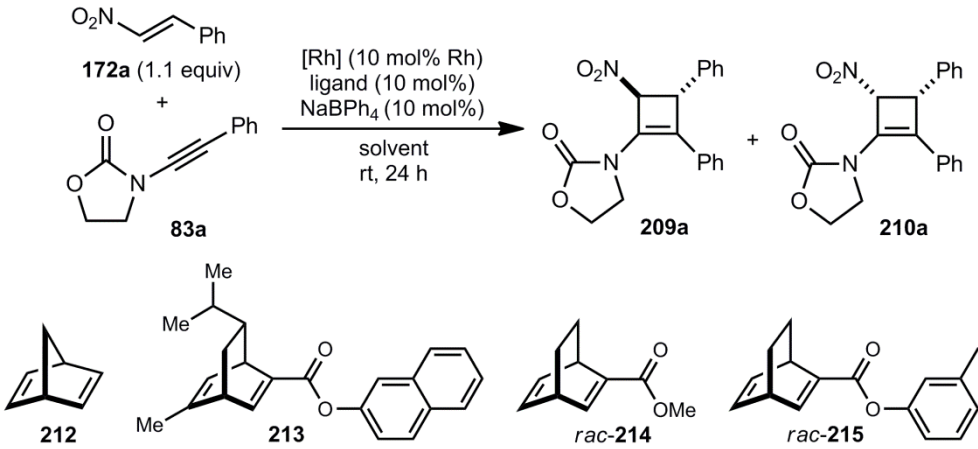


Scheme 4.15

In addition, the diastereomeric ratio obtained from the catalytic organoboron experiment was similar to that obtained when using one equivalent of sodium tetraphenylborate. A catalytic amount of organoboron reagent was utilised for all further cycloaddition reactions to reduce unnecessary waste.

Further optimisation reactions were then carried out to try to improve upon the conversion and diastereoselectivity obtained in Scheme **4.15**. These reactions mainly consisted of solvent screening and diene ligand evaluation. Both $[Rh(cod)Cl]_2$ and alternative catalyst systems, using a diene ligand in combination with $[Rh(C_2H_4)Cl]_2$, were investigated and a summary of these ligand evaluation reactions are shown in Table **4.1**. Unfortunately, it was not initially clear what solvent would be the most suitable for use with each catalytic system, so a mixture of solvent combinations are shown in Table **4.1**.

Table 4.1: Ligand Screening[a]



Entry	[Rh] (5 mol%)	Ligand	Solvent	Conv (%)[b]	dr[b]
1	$[Rh(cod)Cl]_2$	—	10:1 THF/MeOH	66	67:33
2[c,d]	$[Rh(C_2H_4)Cl]_2$	**212**	THF	3	-
3	$[Rh(C_2H_4)Cl]_2$	**213**	10:1 CH_2Cl_2/MeOH	>90	69:31
3	$[Rh(C_2H_4)Cl]_2$	**213**	20:2:1 THF/MeOH/NEt_3	60	84:16
4[c]	$[Rh(C_2H_4)Cl]_2$	**214**	83:1 THF/NEt_3	64	85:15
5	$[Rh(C_2H_4)Cl]_2$	*rac*-**215**	20:2:1 THF/MeOH/NEt_3	>90	87:13

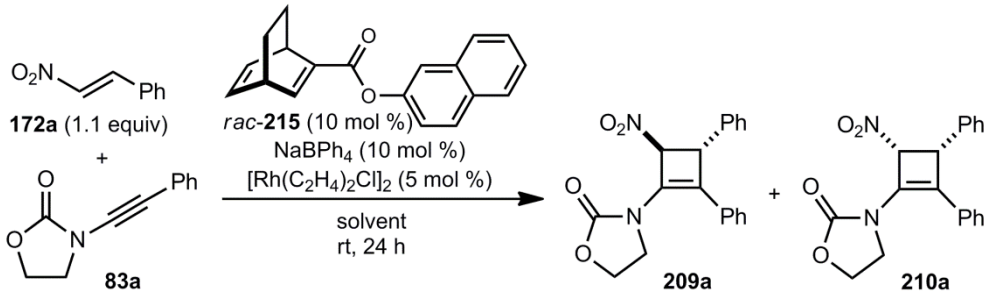
[a] Reactions conducted using 0.30 mmol of **83a**. [b] Determined by ^{1}H NMR analysis of the unpurified reaction mixtures. [c] Reaction was conducted on 0.1 mmol scale. [d] Reaction was conducted using 5 mol% Rh.

Despite initial successes with $[Rh(cod)Cl]_2$, this pre-catalyst was found to provide only unsatisfactory conversions of the ynamide on a 0.3 mmol scale when using 10 mol% $NaBPh_4$ (entry 1). Bicyclic diene **212** was tried as a ligand for rhodium (entry 2), but these conditions provided almost no reaction of the ynamide and thus **212** was deemed unsuitable for use. Chiral diene **213**, reported by Hayashi and co-workers,[108] has previously been investigated as a ligand for rhodium within our research group, and this α-phellandrene-derived ligand (**213**) initially provided promising results in the [2+2] cycloaddition reaction (entry 3). However, when using ligand **213** under different solvent conditions, designed to improve the diastereoselectivity through the addition of triethylamine, conversion of **83a** was much lower (for example entry 4). It was also established that **213** provided only racemic products, thus to avoid unnecessary complexity in the ligand, diene **214** and diene **215**, a racemic analogue of **213**, were synthesised. Employment of diene **214** resulted in incomplete conversion of the ynamide when used in a trial reaction (entry 4); however, it is

possible that alteration of the solvent used may have improved this conversion. Diene **215** resulted in complete conversion of the ynamide (entry 5) when the reaction was conducted in a THF/MeOH/NEt_3 solvent system, and this ligand also appeared more amenable to the use of other nitroalkene or ynamide substrates. Therefore, diene **215** was used as the ligand for the remainder of the [2+2] cycloaddition reactions.

Some solvent screening results, using ligand **215**, are shown in Table **4.2**. These reactions are reported in order to highlight more efficiently the suitability, in terms of both conversion and diastereoselectivity, of a THF/MeOH/NEt_3 solvent combination for the [2+2] cycloaddition reaction.

Table 4.2: Solvent Screening[a]



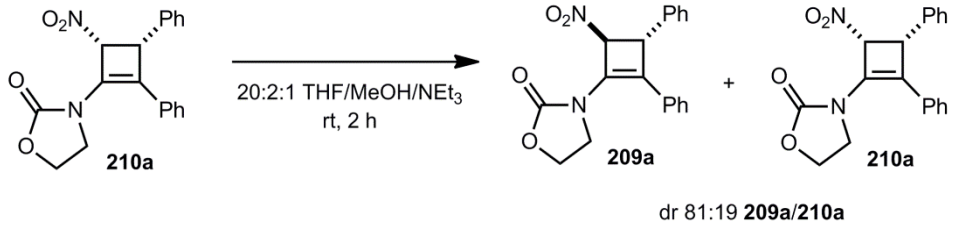
Entry	Solvent	Solvent Ratio	Conv	dr[b]
1	CH_2Cl_2	-	>90	32:68
2	CH_2Cl_2/NEt_3	10:1	39	84:16
3	CH_2Cl_2/MeOH/ NEt_3	10:1:1	88	81:19
4	THF/MeOH/ NEt_3	10:1:1	>90	84:16
5[c]	THF/MeOH	10:1	>90	82:18
6	THF/MeOH/ NEt_3	9:1:3	68	84:16

[a] Reactions conducted using 0.10 mmol of **83a**. [b] Determined by ^{1}H NMR analysis of the unpurified reaction mixtures. [c] Reaction conducted with added K_2CO_3 (0.2 equiv).

In initial work, toluene, dichloroethane, 1,4-dioxane and acetonitrile were all found to be unsuitable solvents for the rhodium-catalysed [2+2] cycloaddition reaction, but the use of dichloromethane as the solvent, under the conditions in Table **4.2**, resulted in complete conversion of the ynamide (entry 1). With dichloromethane and ligand **215**, moderate diastereoselectivity in favour of the *cis* isomer was obtained. The addition of triethylamine improved the diastereomeric ratio in favour of the *trans*

isomer, but also had a detrimental effect on the conversion (entry 2 *vs* 1). Using methanol in combination with triethylamine was much more favourable (entry 3 *vs* 2). Complete conversion was then achieved when THF was chosen for the main reaction solvent, rather than dichloromethane (entry 4 *vs* 3). An inorganic base, K_2CO_3 could also be used to improve the diastereoselectivity (entry 5), but this was slightly less effective than using triethylamine (entry 4) and it was also thought preferable to have a homogenous reaction mixture. Increasing the ratio of triethylamine was found to adversely affect conversion (entry 6), thus, the solvent combination of Table **4.1**, entry 5 was chosen for future reactions.

It was later proven that triethylamine increases the diastereomeric ratio through base promoted equilibration towards the thermodynamic ratio (Scheme **4.16**). Isolated *cis* cyclobutenamide **210a** was subjected to the standard reaction solvent mixture over two hours, and this provided an 81:19 diastereomeric mixture of **209a** and **210a**. This ratio is comparable with the diasteromeric ratios obtained when utilising triethylamine in Table **4.2** above.



Scheme 4.16

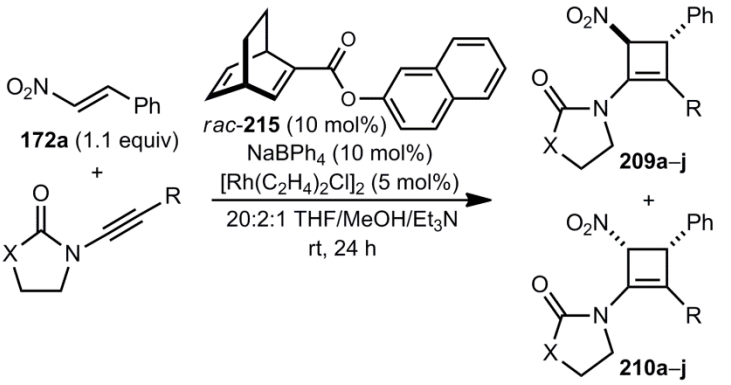
With selection of the catalyst system and solvent mixture now accomplished, the generality of the developed process was investigated in relation to the ynamide and nitroalkene substrate scope.

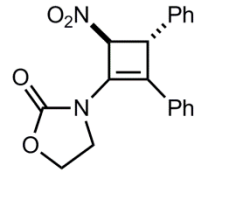
4.2.2 Exploration of the Ynamide Scope

A variety of ynamides were reacted with *trans*-β-nitrostyrene under the standard reaction conditions, to explore the ynamide scope of the cycloaddition reaction (Table **4.3**). It became apparent that for the majority of aryl-substituted ynamides the

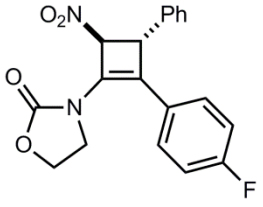
two diastereomeric products could be separated by column chromatography, but for aliphatic-substituted ynamides complete separation was much more difficult and isolating the cycloaddition products as a diastereomeric mixture was more practical.

Table 4.3: Ynamide Scope[a]

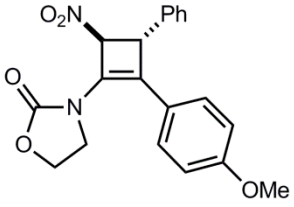




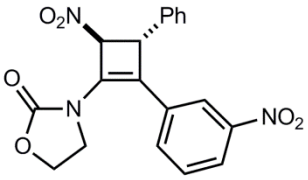
87:13 dr
60% **209a**
14% **210a**



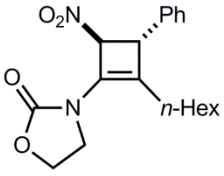
81:19 dr
59% **209b**
14% **210b**



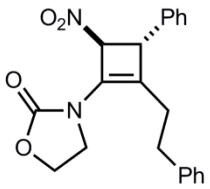
87:13 dr
55% **209c**
15% **210c**



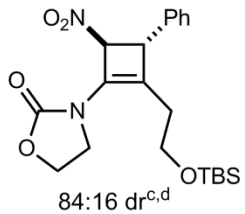
81:19 dr[b]
48% **209d+210d**



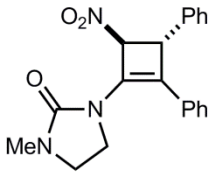
85:15 dr
77% **209e+210e**



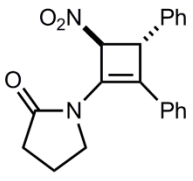
87:13 dr
59% **209f+210f**



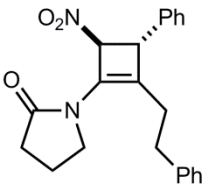
84:16 dr[c,d]
63% **209g+210g**



89:11 dr[c,d]
55% **209h**
8% **210h**



87:13 dr[c]
62% **209i**
16% **210i**



82:18 dr[c,e]
41% **209j+210j**

[a] Reactions were conducted on a 0.3 mmol scale. Diastereomeric ratios were determined by ^{1}H NMR spectroscopy of the unpurified reaction mixtures. [b] Ratio of **209d**:**210d** in isolated product was 83:17. [c] Reaction was conducted at 40 °C. [d] Reaction time was 6 h. [e] Ratio of **209j**:**210j** in isolated product was 90:10.

A high overall yield was obtained for the majority of the reactions in Table **4.3**, although some less reactive ynamide substrates required a higher temperature for an acceptable conversion to be reached within 24 hours. Additionally, the crude diastereomeric ratio was maintained above 80:20 for all of the reactions reported in Table **4.3**, which shows the developed reaction conditions to indeed be applicable to a range of ynamides. Both aromatic and aliphatic-substituted ynamides were found to be successful substrates for the reaction (**209**/**210a**-**209**/**210j**), however, use of 3-nitrophenyl ynamide **83j** did result in a lower yield being obtained (**209**/**210d**), and some decomposition of the desired product was apparent. A comparison of different phenyl-substituted ynamides revealed that oxazolidinone ynamide **83a** results in a higher yield and a more favourable diastereomeric ratio (**209**/**210a**) than its imidazole equivalent (**209**/**210h**). Additionally, both of these ynamides (**83a** and **83m**) showed a higher affinity for the developed cycloaddition reaction than pyrrolidinone ynamide **83f**, for which although a high yield was achieved (**209**/**210i**), an elevated reaction temperature was required for full ynamide conversion to occur. Pyrrolidinone ynamide **83e** also proved less reactive than its oxazolidinone equivalent (**83c**) towards the [2+2] cycloaddition and complete conversion of ynamide **83e** was still not achieved at a temperature of 40 °C. Hence, a lower yield was obtained when utilising this pyrrolidinone ynamide (**209**/**210j**) than for the other reactions in Table **4.3**. Repetition of the reaction involving ynamide **83e** at an even higher temperature was not attempted as, in general, the cyclobutenamide products were observed to undergo some decomposition at 65 °C.

Further investigation into the reaction scope unfortunately revealed that ynamides where the nitrogen atom is not part of a cyclic system (Figure **4.1**) provide little or no conversion to the desired cyclobutenamide products under the standard reaction conditions. Reaction of each of the ynamides shown in Figure **4.1** with *trans*-β-nitrostyrene was attempted, but with little success.

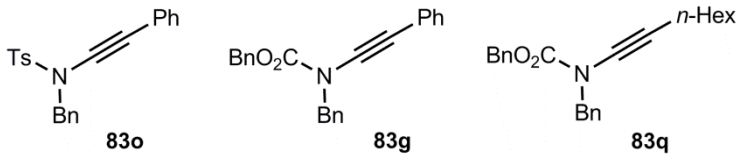
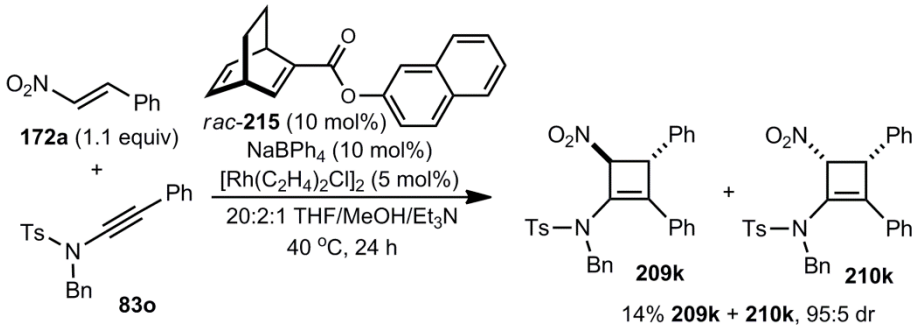


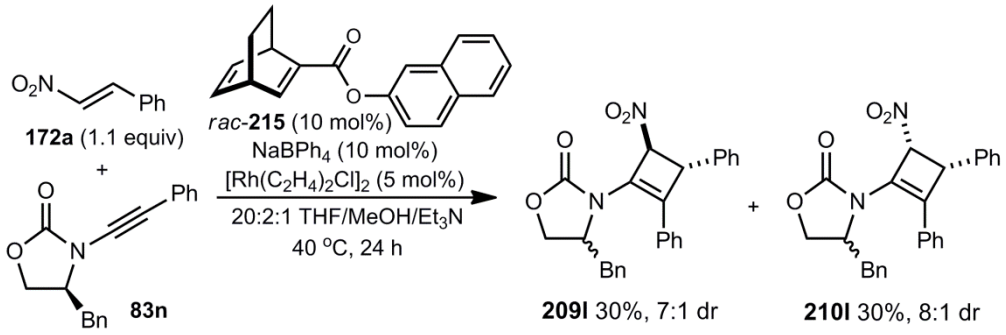
Figure 4.1

The most successful reaction using one of the ynamides from Figure **4.1** is shown in Scheme **4.17**. The reaction provided 28% conversion to the desired products and a crude diastereomeric ratio of 94:6 *trans* (**209k**) to *cis* (**210k**). The products were able to be isolated as a diastereomeric mixture, but the resulting yield was found to be very low.



Scheme 4.17

In a [2+2] cycloaddition reaction of **83n** with *trans*-β-nitrostyrene, full consumption of ynamide **83n**, containing a chiral centre, was achieved by increasing the temperature that the reaction was conducted at to 40 °C, rather than room temperature (Scheme **4.18**).



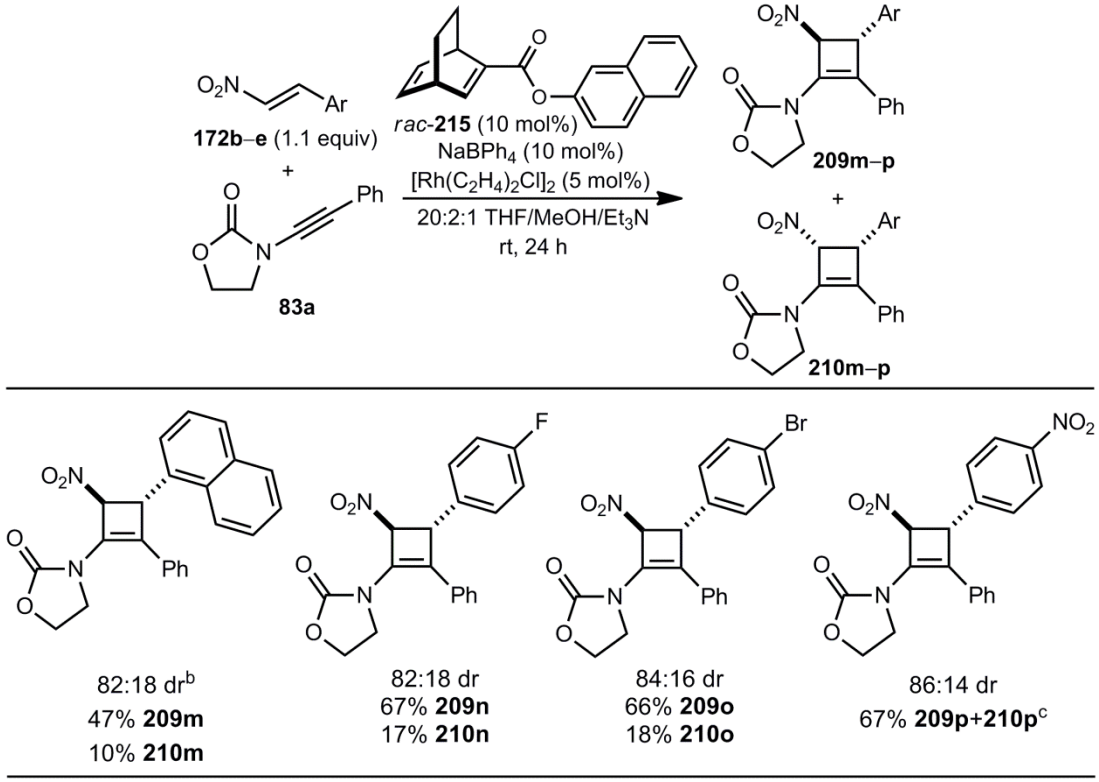
Scheme 4.18

Interestingly, reaction of ynamide **83n** with *trans*-β-nitrostyrene provided a 1:1 mixture of *trans* (**209l**) and *cis* (**210l**) cyclobutenamide diastereomers. Unfortunately products **209l** and **210l** could not be isolated cleanly as a single isomer, and which diastereomer with respect to the benzyl group orientation was the major product in each case was unknown.

4.2.3 Exploration of the Nitroalkene Scope

The nitroalkene scope of the developed [2+2] cycloaddition reaction was briefly explored using ynamide **83a** as a model substrate (Table **4.4**).

Table 4.4 Nitroalkene Scope[a]



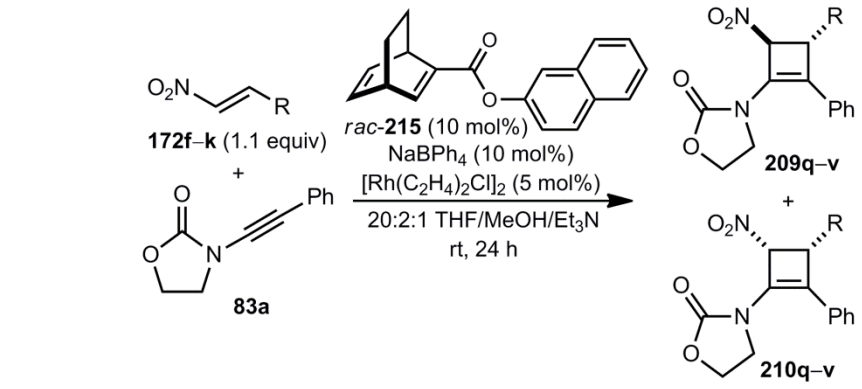
[a] Reactions were conducted on a 0.3 mmol scale. Diastereomeric ratios were determined by ^{1}H NMR spectroscopy of the unpurified reaction mixtures. [b] Reaction was conducted at 40 °C for 6 h. [c] Ratio of **209p**/**210p** in isolated product was 81:19.

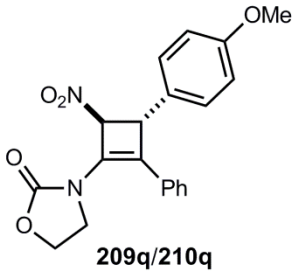
The nitroalkenes selected for initial scope investigation (Table **4.4**) provided good overall yields of the desired products and crude diastereomeric ratios consistent with those previously observed (Table **4.3**). The use of 1-[(*E*)-2-nitroethenyl]naphthalene

required an increased reaction temperature due to the increased steric bulk surrounding the alkene reaction partner, and for the same reason, the products of this reaction (**209**/**210m**) were more susceptible to degradation than the other Table **4.4** products, and hence a lower overall yield was obtained. Nitroalkenes that include *para*-halogen substituents were found to be successful substrates for the [2+2] cycloaddition reaction (**209**/**210n**, **209**/**210o**). Although 1-nitro-4-[(*E*)-2-nitroethenyl]benzene underwent the reaction successfully, the diastereomeric products could not be fully separated by column chromatography and **209**/**210p** were isolated as a diastereomeric mixture. The difficult separation of cyclobutenamide diastereomers that contain two nitro groups appears to be a recurrent issue (see **209**/**210d**).

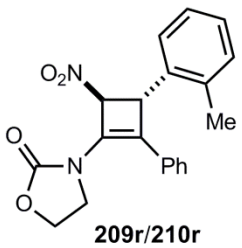
Following the initial success in variation of the nitroalkene coupling component, a further selection of nitroalkenes was investigated for use in a [2+2] cycloaddition with ynamide **83a**. However, for these substrates the desired cyclobutenamide products could unfortunately not be obtained using the developed reaction conditions (Table **4.5**).

Table 4.5: Further Nitroalkenes

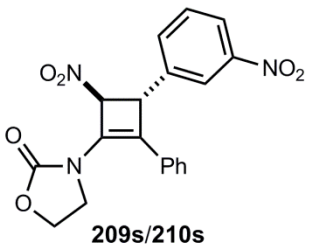




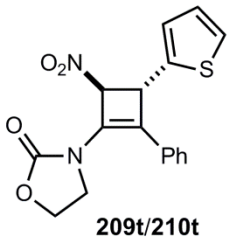
209q/210q
78:22 dr
85% conv



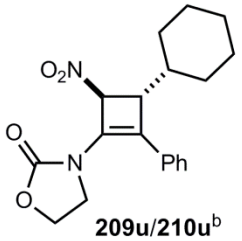
209r/210r
73:27 dr
43% conv



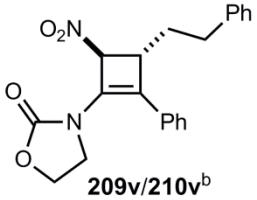
209s/210s
81:19 dr
17% conv



209t/210t
78:22 dr
49% conv



209u/210u[b]
n.d
10% conv



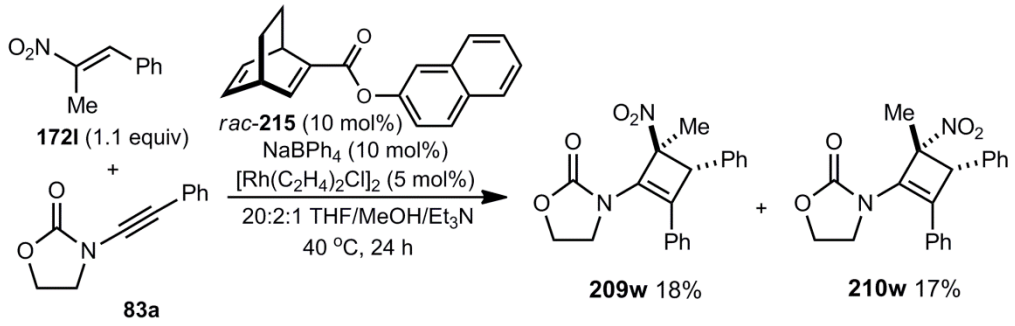
209v/210v[b]
86:14 dr
25% conv

[a] Reactions were conducted on 0.3 mmol scale. Diastereomeric ratios were determined by ^{1}H NMR spectroscopy of the unpurified reaction mixtures. [b] Reaction conducted at 40 °C.

A high conversion of ynamide **83a** occurred when 1-methoxy-4-[(*E*)-2-nitroethenyl]benzene was employed as the coupling partner. However, the cyclobutenamide products (**209**/**210q**) could not be isolated as significant decomposition of the products occurred on attempted purification. Reaction of **83a** with an *ortho*-substituted nitroalkene provided only low conversion to the desired products, presumably due to steric hindrance (**209**/**210r**). The nitroalkene 1-nitro-3-[(*E*)-2-nitroethenyl]benzene had been expected to be an acceptable substrate, based on the success of **209**/**210p**, but unfortunately this was not the case and only very low conversion to cyclobutenamides **209**/**210s** was observed. The [2+2] cycloaddition of ynamide **83a** and a thiophene-substituted nitroalkene was subject to

an unidentified competing side reaction, thus the conversion to cyclobutenamides **209**/**210t** was only moderate. Attempted separation of the desired cyclobutenamide (**209t**) from the side product was unsuccessful, thus **209t** could not be isolated and the side product could not be identified. Aliphatic nitroalkenes were found to be unsuitable substrates for [2+2] cycloaddition with ynamides as conversions were very low, even at 40 °C. Attempted isolation of product **209v**, from the reaction of [(3*E*)-4-nitrobut-3-en-1yl]-benzene, was unsuccessful as starting ynamide **83a** could not be fully separated from the product.

We wanted to investigate the use of 1,2-disubstituted nitroalkenes as reaction partners for the [2+2] cycloaddition of ynamides as there is a higher chance of developing an enantioselective version of the reaction with these substrates. Contrary to the other nitroalkenes used in this study, nitroalkenes such as **172l** do not possess a hydrogen that is α to the nitro group, meaning that interconversion of the diastereomeric products and thus epimerisation of a chiral centre at this α position would be prevented. Reaction of ynamide **83a** with nitroalkene **172l** was attempted and only 32% conversion to the desired products (**209w**/**210w**) occurred. Conducting the reaction at 40 °C resulted in complete consumption of the ynamide occurring, but only a low yield of the cycloaddition products were obtained (Scheme **4.19**).



Scheme 4.19

The resultant 1:1 ratio of *trans*/*cis* products after product isolation was presumably due to the inability of triethylamine to promote base-catalysed equilibration in this case. The diastereomeric ratio of the crude reaction mixture could not be accurately determined from the corresponding ^{1}H NMR spectrum and the *trans*/*cis* geometries

of the respective products were confirmed by NOESY spectroscopy after isolation. The low yields in Scheme **4.19** could be a consequence of product decomposition under the reaction conditions, due to the increased steric hindrance surrounding the cyclobutene ring.

4.2.4 Structural Determinations

A crystal structure was obtained of the major product (**209b**) from the [2+2] cycloaddition reaction between ynamide **83i** and *trans*-β-nitrostyrene (Figure **4.2**).

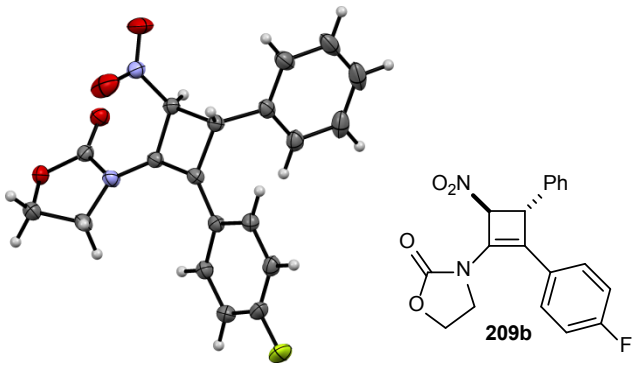


Figure 4.2[*]

This crystal structure confirmed the major product (**209b**) to be of the anticipated cyclobutenamide structure, and to have a *trans* relationship between the protons α and β to the nitro group. All other major products from the developed [2+2] cycloaddition reaction were assigned as the *trans* diastereomer and the minor products assigned as the *cis* diastereomer by analogy.

The assignment of *trans* or *cis* geometry was further assisted by analysis of the alkene region of the ^{1}H NMR spectrum of each cyclobutenamide product obtained. Distinct differences between the ^{1}H NMR spectra of the *trans* and *cis* isomers were exhibited for all of the cyclobutenamide products, mainly the magnitude of the coupling constant between the protons α and β to the nitro group and the chemical shift of these protons. For cyclobutenamides obtained from aryl-substituted ynamides

[*] Dr Gary S. Nichol of The University of Edinburgh is acknowledged for X-ray crystallography.

(see Figure **4.3**), the coupling constant between the protons α and β to the nitro group was found to be typically 1.3 Hz when these protons are in a *trans* orientation (**209a**), but much larger, typically 5.2 Hz, when these protons are in a *cis* orientation (**210a**). In general, the chemical shifts of both the α and β protons were found to be 0.35-0.5 Hz higher for a *cis* cyclobutenamide than for the corresponding *trans* product.

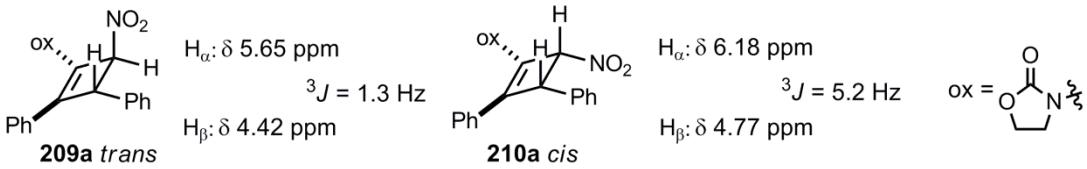
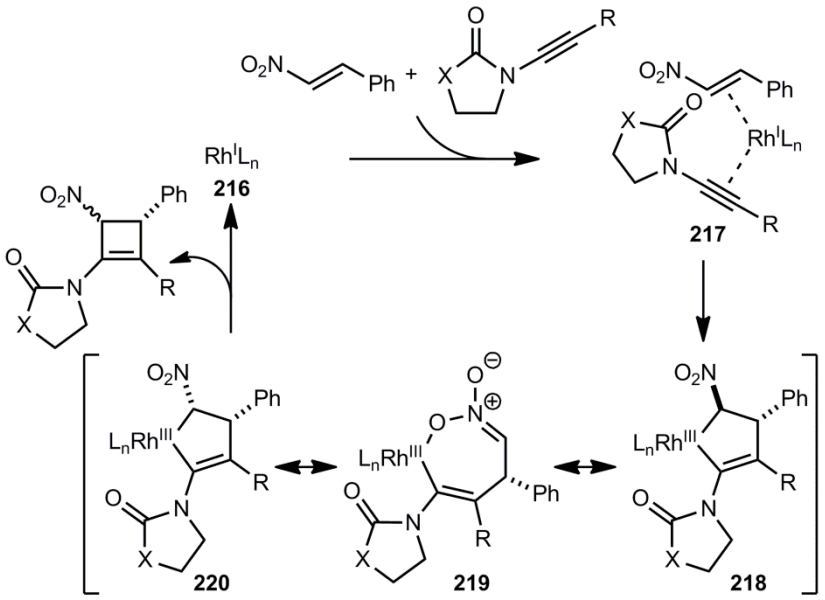


Figure 4.3

The observed difference in the coupling constants should be expected as the magnitude of a coupling constant is dependent not only on the distance between the coupling nuclei but also on the relevant dihedral angle. The Karplus equation[109] tells us that a dihedral angle close to 0° between two protons in a ^3J coupling system will result in a large coupling constant and an angle nearer 90° will result in a low coupling constant.[110] Thus, the *cis* cyclobutenamide should indeed have a much larger coupling constant than the *trans* isomer (Figure **4.3**). In addition, a publication by Fleming and Williams,[111] describing the NMR spectra of 4-membered carbocyclic rings, reported the coupling constants in a similar cyclobutene system to be 2 Hz for the protons in a *trans* relationship and 6 Hz for the *cis* relationship, which corresponds well to the values observed for the cyclobutenamide products.

4.3 Mechanism

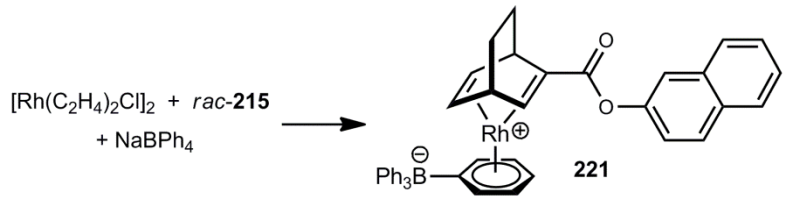
The proposed mechanism of the rhodium-catalysed [2+2] cycloaddition reaction of ynamides with nitroalkenes is shown in Scheme **4.20**. The mechanism is believed to occur via rhodacycle **218** (similar five-membered metallocycles involving ynamides have previously been reported[112]).



Scheme 4.20

The mechanism proceeds through coordination of both the nitroalkene and the ynamide to rhodium(I) (**217**). Then oxidative cyclisation occurs, forming 5-membered rhodacycle **218**. The rhodacycle may be able to interconvert between the *trans* (**218**) and *cis* (**220**) forms, as shown, via coordination to the nitro group (**219**). Reductive elimination then occurs on either the *trans* or *cis* rhodacycle to provide the [2+2] cycloaddition product.

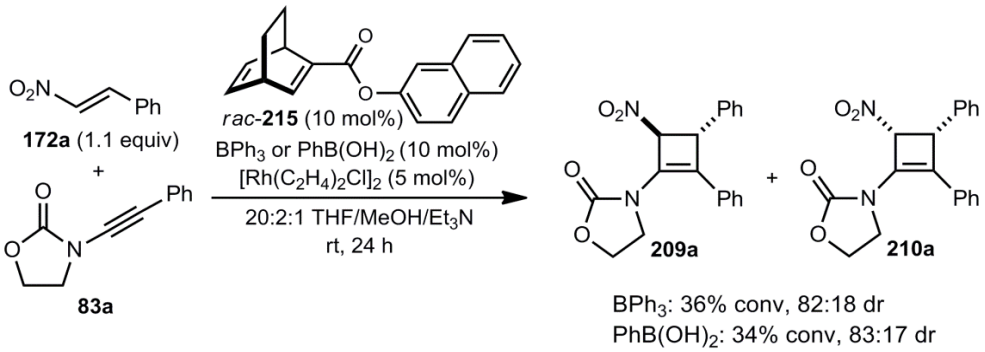
The nature of rhodium(I) species **216** and the role of the necessary organoboron reagent in the developed [2+2] cycloaddition reaction remain unexplained by the above mechanistic cycle (Scheme **4.20**). An investigation into the identity of the active catalyst (**216**) was attempted. Firstly, as the [2+2] cycloaddition reaction does not occur without the organoboron reagent, it is most likely that $NaBPh_4$ is involved in the formation of species **216**. It was established that $NaBPh_4$ was not simply acting by anionic exchange at the rhodium centre, as replacement of $NaBPh_4$ with $AgBF_4$ or NH_4PF_6 resulted in no reaction occurring. From literature precedent,[113] it appeared likely that $NaBPh_4$ is involved through coordination of one of the phenyl rings of $NaBPh_4$ to the rhodium centre (Scheme **4.21**).



Scheme 4.21

The reaction components $[Rh(C_2H_4)_2Cl]_2$, ligand **215** and $NaBPh_4$ can initially react together to form Rh(**215**)(η_6-C_6H_5)BPh_3 (**221**). However, whether **221** is the active catalyst species itself or whether it is further transformed into the active catalyst remains unclear. Unfortunately, attempts to isolate the proposed active complex (**221**) were unsuccessful.

If **221** is indeed formed during the developed [2+2] cycloaddition of ynamides, then triphenylborane or phenylboronic acid could be suitable additives for the reaction, as they also possess a phenyl ring bonded to a boron atom. Reactions were conducted where sodium tetraphenylborate was replaced with either triphenylborane or phenylboronic acid (Scheme **4.22**), and both of these reactions resulted in moderate conversion to the cycloaddition products.



Scheme 4.22

Alternatively, other suggestions for the identity of the active rhodium catalyst (**216**) that were largely discounted were that an arylated ynamide or an arylated nitroalkene were acting as a ligand for the rhodium (**222** or **223** respectively). These species would be formed through rhodium mediated arylation of the respective substrate with sodium tetraphenylborate, perhaps even proceeding through species **221**.

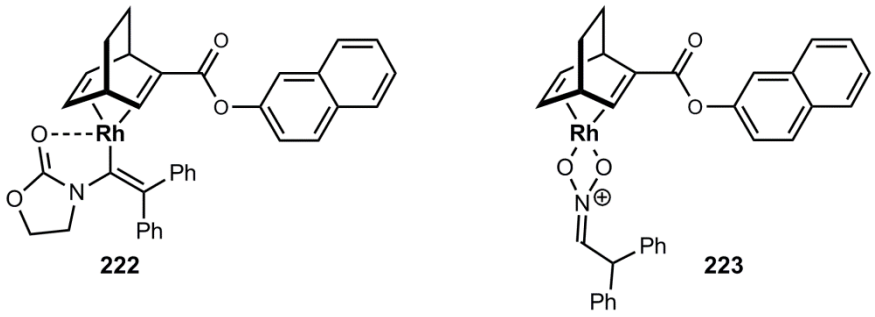
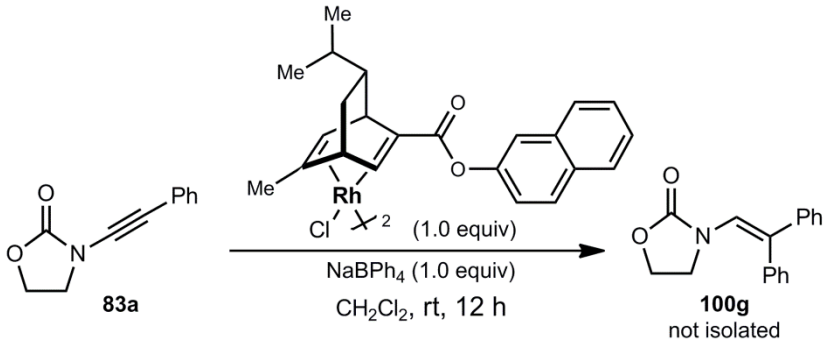


Figure 4.4

A previous publication from our group described the rhodium-catalysed arylation of ynamides using organoboron reagents.[59] Rhodium species **222** is very similar in structure to an alkenylrhodium intermediate strongly believed to occur during this previously developed ynamide arylation reaction. In order to investigate the presence of species **222** within the course of the developed [2+2] cycloaddition reaction, the occurrence of corresponding enamide **100g** was monitored. If species **222** is the active catalyst then it was expected that enamide **100g** would be formed upon work up of the reaction mixture. Enamide **100g** had previously been observed by my collaborator Suresh Reddy Chidipudi, under alternative conditions (Scheme **4.23**) that used a preformed rhodium-diene species, but the product was not isolated.

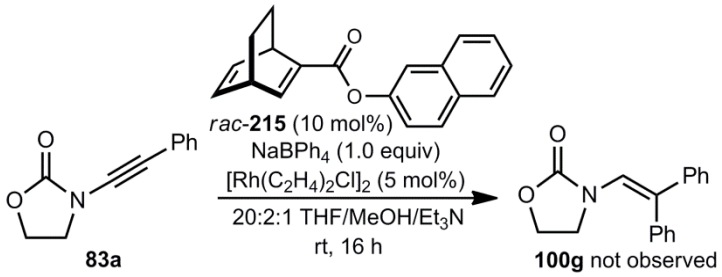


Scheme 4.23[*]

However, enamide **100g** was not observed during analysis of the ^{1}H NMR spectra of the crude reaction mixtures of the [2+2] cycloaddition reactions involving ynamide **83a** that were reported in Table **4.3** or Table **4.4**. In addition, enamide **100g** was not

[*] This reaction was carried out by Suresh Reddy Chidipudi.

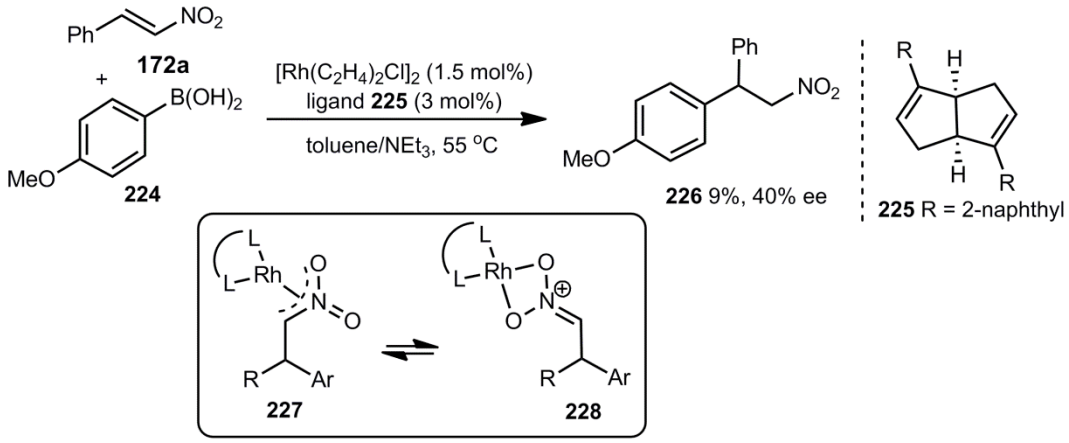
observed when one equivalent of sodium tetraphenylborate was used to try and increase the production of enamide **100g** (Scheme **4.24**).



Scheme 4.24

It can be concluded that either species **222** is not the active catalyst for our [2+2] cycloaddition of ynamides or that the binding of the arylated ynamide-type ligand to the rhodium centre is strong and thus the ligand remains attached to the rhodium during work up and consequently enamide **100g** is not observed in the crude reaction mixture.

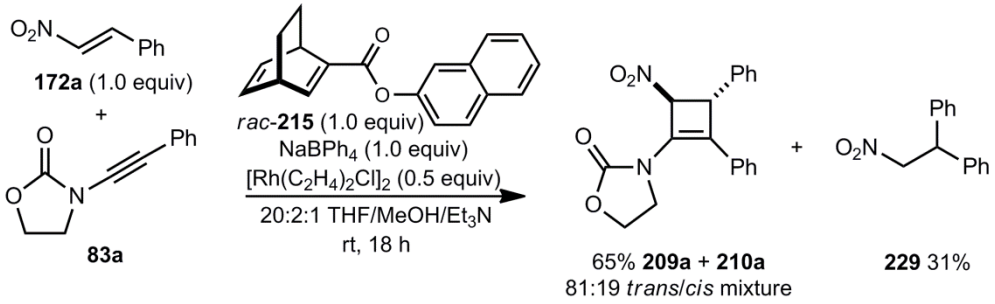
It is known that nitroalkenes can be arylated by organoboron reagents using rhodium catalysis.[114] In a publication by Xu and co-workers, conditions that are not dissimilar to our own standard reaction conditions produced nitroalkane **226** in a low yield (Scheme **4.25**).



Scheme 4.25

The low yield of **226** was attributed to the stability of rhodium nitronate intermediates **227**/**228**, preventing catalyst turnover and release of the product (**226**). Subsequent alteration of the reaction conditions caused catalyst turnover to occur and high yields of the desired products were obtained by Xu and co-workers. However, the apparent stability of rhodium-nitronate intermediate **228** initiated the idea that a nitronate ligand could be involved in the active catalyst species of our developed cycloaddition reaction.

If a nitronate ligand is involved in the [2+2] cycloaddition (**223**, Figure **4.4**), then nitroalkene arylation products, such as **229**, could be expected to be present in the reaction mixture. Nitroalkane **229** was indeed found to be present in a number of reaction mixtures, including that of a reaction using stoichiometric rhodium (Scheme **4.26**).



Scheme 4.26

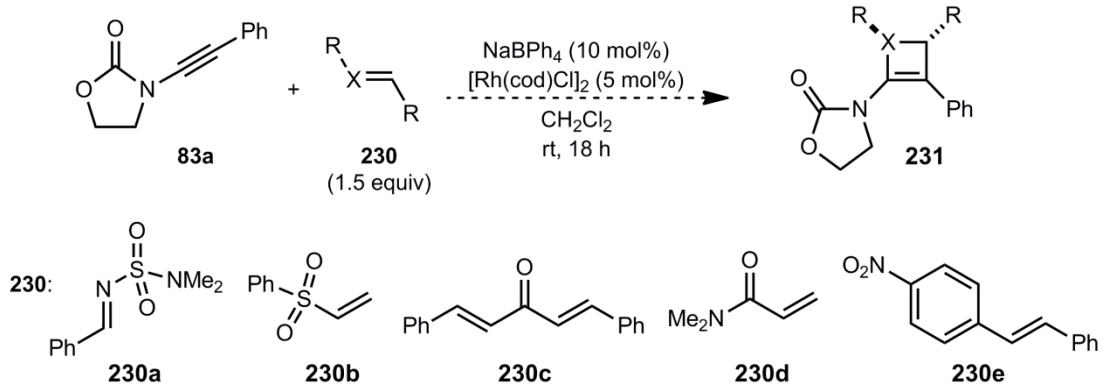
However, it was later concluded that **229** is likely produced as a side product in competition with the desired [2+2] cycloaddition reaction, through a reaction similar to that of Scheme **4.25**, rather than as a consequence of the corresponding nitronate (**223**) having involvement as a ligand for the rhodium. This tentative conclusion was reached due to **229** not being formed quantitatively in Scheme **4.26** and due to the greater tendency for **229** to be observed in those reactions conducted at a higher temperature, where an increase in side reactions would be expected.

Overall, it was concluded that complex **221**, where a phenyl ring of tetraphenylborate coordinates to the rhodium, is highly likely to be formed prior to the [2+2]

cycloaddition reaction commencing, and this gives some explanation for the requirement of using an organoboron reagent in the developed cycloaddition reaction. However, whether **221** is then transformed into a further active catalyst species remains unclear.

4.4 Alternative Substrates

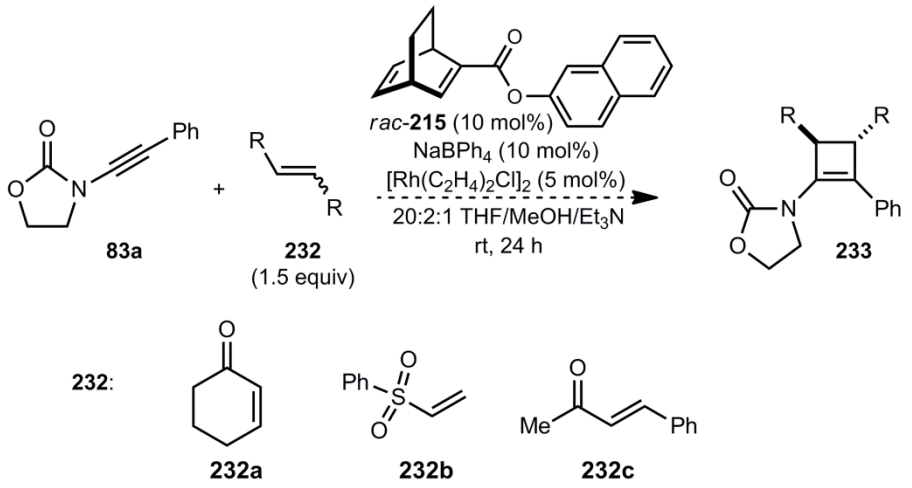
Previous to the [2+2] cycloaddition reaction conditions being standardised, a number of alternative cycloaddition partners were tried in reaction with ynamide **83a**, using $[Rh(cod)Cl]_2$ as the catalyst (Scheme **4.27**).



Scheme 4.27

An imine (**230a**) and alkenyl moieties with an electron withdrawing or electron poor group attached, such as phenyl vinyl sulfone (**230b**) or dibenzylideneacetone (**230c**), were tried as [2+2] cycloaddition substrates, but unfortunately no desired product was observed in any of the trial reactions.

After the development of the standard reaction conditions for [2+2] cycloaddition of ynamides with nitroalkenes, the use of an alternative reaction partner was briefly explored again (Scheme **4.28**).



Scheme 4.28

This time the cyclohexanone (**232a**) used by Hsung and co-workers[103a] was included as a possible substrate, along with phenyl vinyl sulfone (**232b**) and benzylideneacetone (**232c**). However, no reaction occurred with any of the alternative substrates in Scheme **4.29**. It was concluded likely that only nitroalkenes are suitable [2+2] cycloaddition partners for ynamides under the standard reaction conditions, and that the use of alternative substrates would require the development of alternative reaction conditions.

4.5 Conclusions

The first metal-catalysed [2+2] cycloaddition reaction of ynamides with nitroalkenes has been developed. This procedure will help to expand on the currently limited literature regarding cycloaddition reactions of ynamides with electron-deficient alkenes. The newly developed method uses a combination of rhodium(I) and an organoboron reagent to promote the reaction, which is a catalyst system that has been relatively unexplored in the literature, and may guide the development of future rhodium-catalysed procedures.

Highly-functionalised, novel cyclobutenamide products have been obtained in good yield, and with a diastereoselectivity that favoured the *trans* isomer. Previous reported cyclobutenamide syntheses have largely provided *cis* isomers of the product

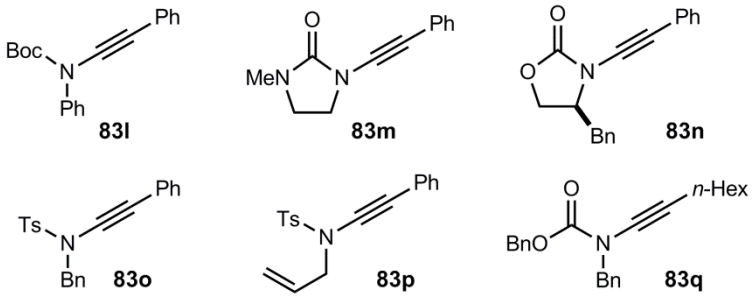
so a consistent route to *trans* cyclobutenamides is now available. A large number of ynamides were found to undergo the reaction successfully, but there were some limitations of the method identified, as some nitroalkenes, including alkyl-substituted nitroalkenes, provide only low conversions at present.

Future work relating to the newly developed [2+2] cycloaddition of ynamides with nitroalkenes, could be to further define the mechanism of the reaction with a view to developing a means of rendering the reaction enantioselective or expanding the scope of the reaction to other substrate classes. Perhaps boron or rhodium NMR could assist with further mechanism exploration. Additionally, investigation into synthetic transformations of the cyclobutenamide products would be a worthwhile endeavour, but if the cyclobutene ring is to remain intact then these transformations would have to occur under mild conditions.

5. Experimental

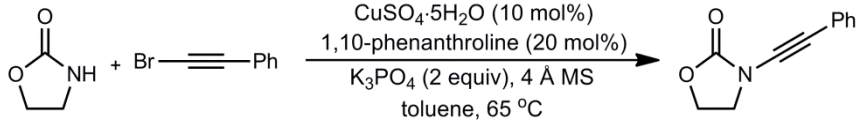
All reactions were carried out under a nitrogen atmosphere. THF, toluene, Et_2O, CH_2Cl_2 and methanol were dried and purified by passage through activated alumina columns using a solvent purification system from http://www.glasscontoursolventsystems.com. All commercially available reagents were used as received. Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien $60F_{254}$ 0.2 mm precoated plates. Product spots were visualized by UV light at 254 nm, and subsequently developed using a vanillin solution. Flash column chromatography was carried out using silica gel (Fisher Scientific 60Å particle size 35-70 micron) employing the method of Still and co-workers.[115] Melting points are uncorrected. Infra-red spectra were recorded as a solid or a thin film on a Shimadzu IRAffinity-1 spectrometer. ^{1}H NMR spectra were recorded on a Bruker AVA400 (400 MHz) or Bruker AVA500 (500 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual protonated solvent as internal standard ($CDCl_3$ at 7.27 ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q, (quartet), quin (quintet), app (apparent), m (multiplet), br (broad). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker AVA500 (125.8 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using deuterated solvent as internal standard ($CDCl_3$ at 77.0 ppm). Assignments were made using the DEPT sequence with secondary pulses at 90° and 135°. ^{19}F NMR spectra were recorded on a Bruker AVA400 (376 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of $CFCl_3$ (δ = 0 ppm), using fluorobenzene as internal standard (C_6H_5F at –113.2 ppm). High-resolution mass spectra were recorded using electrospray ionization (ESI), electron impact (EI), or atmospheric solids analysis probe (ASAP) techniques on a Finnigan MAT 900 XP spectrometer, a Finnigan MAT 95 XP spectrometer, or a Thermofisher LTQ Orbitrap XL spectrometer at the EPSRC National Mass Spectrometry Service Centre, University of Wales, Swansea, or on a Finnigan MAT 900 XLT spectrometer at the School of Chemistry, University of Edinburgh.

5.1 Preparation of Ynamides



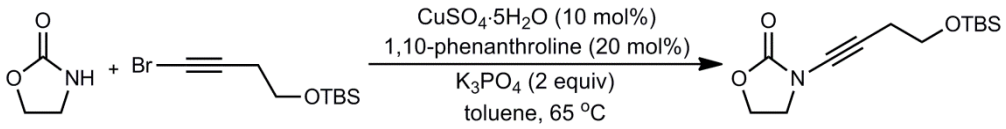
Ynamides **83l**,[33a] **83m**,[33a] **83n**,[60a] **83o**,[33b] **83p**[8] and **83q**[33b] were prepared by other members of the Lam group using previously reported procedures.

3-Phenylethynyloxazolidin-2-one (83a)



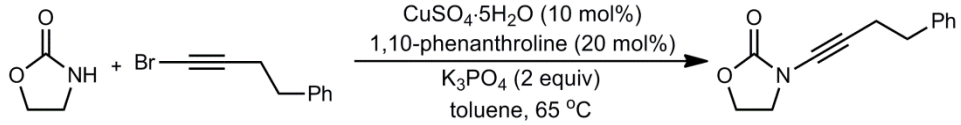
Following a slight modification of the procedure of Hsung and co-workers,[8] a mixture of 1-bromo-2-phenylacetylene (7.93 g, 43.8 mmol), 2-oxazolidinone (3.48 g, 40.0 mmol), K_3PO_4 (17.0 g, 80.0 mmol), $CuSO_4 \cdot 5H_2O$ (999 mg, 4.00 mmol), 1,10-phenanthroline (1.44 g, 8.00 mmol) and 4 Å molecular sieves in toluene (80 mL) was heated at 65 °C for 17 h. After cooling to room temperature, the mixture was filtered through a short pad of silica gel using $CHCl_3$ (100 mL) and then EtOAc (100 mL) as the eluents, and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/hexanes→50% EtOAc/hexane) gave the *ynamide* **83a** (4.37 g, 58%) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48-7.44 (2H, m, Ar**H**), 7.34-7.30 (3H, m, Ar**H**), 4.53-4.49 (2H, m, C**H**$_2$O), 4.05-4.01 (2H, m, C**H**$_2$N); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 155.8 (C), 131.5 (2 × CH), 128.3 (2 × CH), 128.2 (CH), 122.1 (C), 78.9 (C), 76.5 (C), 63.0 (CH_2), 47.0 (CH_2). Spectral data in agreement with literature data.[9]

3-[4-(*tert*-Butyldimethylsilyloxy)but-1-ynyl]oxazolidin-2-one (83b)



Following the procedure of Hsung and co-workers,[8] a mixture of 1-bromo-4-*tert*-butyldimethylsilyloxy-1-butyne (5.37 g, 20.4 mmol), 2-oxazolidinone (1.61 g, 18.5 mmol), K_3PO_4 (7.85 g, 37.0 mmol), $CuSO_4 \cdot 5H_2O$ (462 mg, 1.85 mmol) and 1,10-phenanthroline (667 mg, 3.7 mmol) in toluene (37 mL) was heated at 65 °C for 67 h. After cooling to room temperature, the mixture was filtered through a celite pad using $CHCl_3$ (130 mL) as the eluent, and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/hexane→25% EtOAc/hexane) gave the *ynamide* **83b** (752 g, 15%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.44-4.38 (2H, m, C**H**$_2$O), 3.89-3.84 (2H, m, C**H**$_2$N), 3.72 (2H, t, *J* = 7.2 Hz, C**H**$_2$OSi), 2.51 (2H, t, *J* = 7.2 Hz, ≡CC**H**$_2$), 0.89 (9H, s, SiC(C**H**$_3$)$_3$), 0.06 (6H, s, Si(C**H**$_3$)$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 156.4 (C), 70.9 (C), 68.0 (C), 62.8 (CH_2), 61.8 (CH_2), 46.8 (CH_2), 25.7 (3 × CH_3), 22.6 (CH_2), 18.2 (C), –5.4 (2 × CH_3). Spectral data in agreement with literature data.[33b]

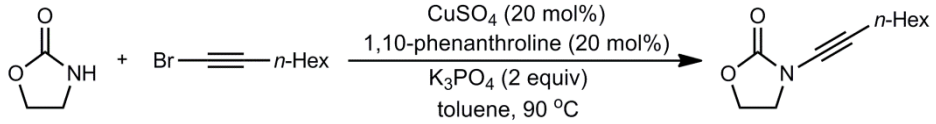
3-(4-Phenylbut-1-ynyl)oxazolidin-2-one (83c)



Following the procedure of Hsung and co-workers,[8] a mixture of 1-bromo-4-phenyl-1-butyne (7.04 g, 33.7 mmol), 2-oxazolidinone (2.67 g, 30.6 mmol), K_3PO_4 (13.0 g, 61.2 mmol), $CuSO_4 \cdot 5H_2O$ (764 mg, 3.06 mmol) and 1,10-phenanthroline (1.10 g, 6.12 mmol) in toluene (50 mL) was heated at 65 °C for 23 h. After cooling to room temperature, the mixture was filtered through a celite pad using $CHCl_3$ (130 mL) as the eluent, and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/hexanes→35% EtOAc/hexane) gave the *ynamide* **83c** (4.19 g, 64%) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.29 (2H, m, Ar**H**), 7.25-7.20 (3H, m, Ar**H**), 4.40 (2H, app. t, *J* = 8.1 Hz, C**H**$_2$O), 3.83 (2H, app. t, *J* = 8.1 Hz, C**H**$_2$N), 2.86 (2H, t, *J* = 7.6 Hz, ≡CC**H**$_2$), 2.61 (2H, t, *J* = 7.6 Hz, C**H**$_2$Ph); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 156.6 (C), 140.4 (C),

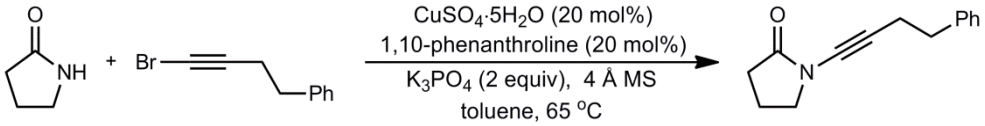
128.4 (2 × CH), 128.3 (2 × CH), 126.3 (CH), 70.6 (C), 70.4 (C), 62.8 (CH_2), 46.8 (CH_2), 35.1 (CH_2), 20.6 (CH_2). Spectral data was agreement with literature data.[33b]

3-Oct-1-ynyloxazolidin-2-one (83d)



In a slight modification of the procedure of Hsung and co-workers,[8] a mixture of 1-bromooctyne (8.50 g, 45.0 mmol), 2-oxazolidinone (3.57 g, 41.0 mmol), K_3PO_4 (17.4 g, 82.0 mmol), $CuSO_4$ (1.31 g, 8.20 mmol) and 1,10-phenanthroline (1.48 g, 8.20 mmol) in toluene (80 mL) was heated at 90 °C for 36 h. After cooling to room temperature, the mixture was filtered through a short pad of silica gel using EtOAc (150 mL) as the eluent, and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography (15% EtOAc/hexanes→40% EtOAc/hexane) gave the *ynamide* **83d** (4.47 g, 56%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.42 (2H, app. t, *J* = 8.0 Hz, C**H**$_2$O), 3.86 (2H, app. t, *J* = 8.0 Hz, C**H**$_2$N), 2.29 (2H, t, *J* = 7.2 Hz, ≡CC**H**$_2$), 1.51 (2H, quintet, *J* = 7.3 Hz, ≡CCH$_2$C**H**$_2$), 1.41-1.23 (m, 6H), 0.88 (3H, t, *J* = 6.9 Hz, C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 156.6 (C), 71.1 (C), 69.9 (C), 62.7 (CH_2), 47.0 (CH_2), 31.3 (CH_2), 28.7 (CH_2), 28.5 (CH_2), 22.5 (CH_2), 18.3 (CH_2), 14.0 (CH_3). Spectral data in agreement with literature data.[9]

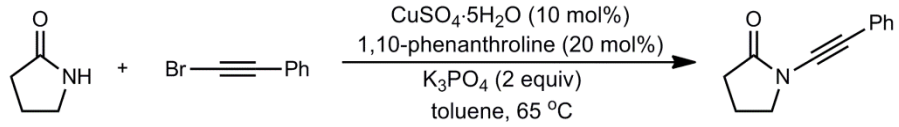
1-(4-Phenylbut-1-ynyl)pyrrolidin-2-one (83e)



Following a slight modification of the procedure of Hsung and co-workers,[8] a mixture of 1-bromo-4-phenyl-1-butyne (4.41 g, 19.8 mmol), 2-pyrrolidinone (1.53 g, 18 mmol), K_3PO_4 (7.64 g, 36 mmol), $CuSO_4 \cdot 5H_2O$ (899 mg, 3.6 mmol), 1,10-phenanthroline (649 g, 3.6 mmol) and 4 Å molecular sieves in toluene (36 mL) was heated at 65 °C for 23 h. After cooling to room temperature, the mixture was filtered through celite pad using $CHCl_3$ (130 mL) as the eluent, and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/hexane→50% EtOAc/hexane) gave the *ynamide* **83e** (1.18g, 31%) as a

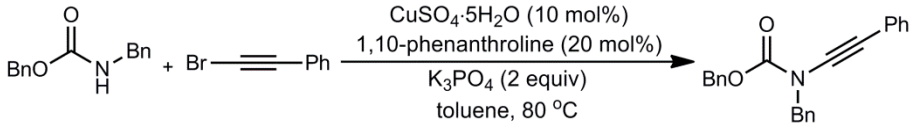
yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.28 (2H, m, Ar**H**), 7.25-7.19 (3H, m, Ar**H**), 3.63 (2H, t, *J* = 7.1 Hz, C**H**$_2$N), 2.86 (2H, t, *J* = 7.6 Hz, C**H**$_2$CH$_2$Ph) and 2.65 (2H, t, *J* = 7.6 Hz, C**H**$_2$Ph), 2.43 (2H, t, *J* = 8.1 Hz, C**H**$_2$C=O), 2.11 (2H, quintet, *J* = 7.5 Hz, C**H**$_2$CH$_2$N); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 176.1 (C), 140.6 (C), 128.5 (2 x CH), 128.3 (2 x CH), 126.2 (CH), 72.0 (C), 71.9 (C), 50.0 (CH_2), 35.3 (CH_2), 29.6 (CH_2), 20.9 (CH_2), 18.7 (CH_2). Spectral data in agreement with literature data.[33b]

1-Phenylethynylpyrrolidin-2-one (83f)



Following the procedure of Hsung and co-workers,[8] a mixture of 1-bromo-2-phenylacetylene (3.47 g, 19.1 mmol), 2-pyrrolidinone (1.48 g, 17.4 mmol), K_3PO_4 (7.39 g, 34.8 mmol), $CuSO_4 \cdot 5H_2O$ (434 mg, 1.74 mmol) and 1,10-phenanthroline (627 mg, 3.48 mmol) in toluene (35 mL) was heated at 65 °C for 48 h. After cooling to room temperature, the mixture was filtered through a celite pad using $CHCl_3$ (100 mL) as the eluent, and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/hexanes→40% EtOAc/hexane) gave the *ynamide* **83f** (765 mg, 19%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.43 (2H, m, Ar**H**), 7.31-7.28 (3H, m, Ar**H**), 3.80 (2H, t, *J*= 7.3 Hz, C**H**$_2$N), 2.49 (2H, dd, *J* = 8.3, 7.6 Hz, C**H**$_2$CO), 2.22-2.13 (2H, m, CH$_2$C**H**$_2$CH$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 175.7 (C), 131.5 (2 × CH), 128.2 (2 × CH), 127.9 (CH), 122.6 (C), 80.4 (C), 72.5 (C), 50.1 (CH_2), 29.7 (CH_2), 18.8 (CH_2). Spectral data in agreement with literature data.[9]

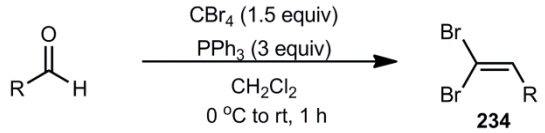
***N*-Benzyl-*N*-phenylethynylcarbamic acid benzyl ester (83g)**



Following a slight modification of the procedure of Hsung and co-workers,[8] a mixture of 1-bromo-2-phenylacetylene (3.13 g, 17.3 mmol), benzylcarbamic acid benzyl ester[116] (3.80 g, 15.7 mmol), K_3PO_4 (6.67 g, 31.4 mmol), $CuSO_4 \cdot 5H_2O$ (392

mg, 1.60 mmol) and 1,10-phenanthroline (566 mg, 3.60 mmol) in toluene (40 mL) was heated at 80 °C for 24 h. After cooling to room temperature, the mixture was filtered through a short pad of silica gel using EtOAc (200 mL) as the eluent, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (5% EtOAc/hexane→10% EtOAc/hexane) to give the *ynamide* **83g** (2.53 g, 47%) as a pale orange solid. R_f = 0.65 (30% EtOAc/hexane); m.p. 50-60 °C; IR (film) 3033, 2948, 2248, 1726 (C=O), 1598, 1442, 1400, 1289, 1231, 901 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47-7.25 (15H, m, Ar**H**), 5.29 (2H, s, C**H**$_2$), 4.75 (2H, s, C**H**$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 155.0 (C), 135.8 (C), 135.6 (C), 130.8 (CH), 128.6 (4 x CH), 128.5 (2 x CH), 128.23 (2 x CH), 128.18 (2 x CH), 128.1 (CH), 127.7 (2 x CH), 127.4 (CH), 123.2 (C), 82.9 (C), 71.5 (C), 68.6 (CH_2), 53.9 (CH_2); Exact mass calcd for $C_{23}H_{23}N_2O_2$ $[M+NH_4]^+$: 359.1754, found: 359.1758.

Preparation of Dibromoalkenes: General Procedure A



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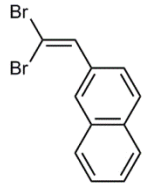
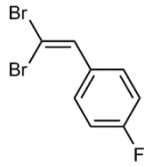
Triphenylphosphine (3 equiv) was added to carbon tetrabromide (1.5 equiv) in CH_2Cl_2 (0.3 M) at 0 ºC. The mixture was stirred for 10 mins at 0 ºC. Aldehyde (x mmol) was then added over a period of 5 mins. Then the reaction mixture was stirred for 1 hour, allowing to warm to room temperature. The mixture was then concentrated *in vacuo*, diluted with hexane and concentrated *in vacuo* a second time. The resulting solid was triturated using 5:1 EtOAc/Hexane (4 x 200 mL). The filtrate was concentrated *in vacuo* and the residue purified by column chromatography to provide the desired dibromoalkene.



2-(2,2-Dibromo-vinyl)napthalene (234a)

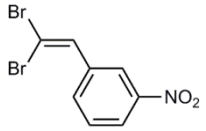
The title compound was prepared according to General Procedure A using 2-naphthaldehyde (6.25 g, 40.0 mmol) and purified by column chromatography (10% EtOAc/hexane) to give a yellow solid (5.8 g, 46%). R_f = 0.63 (10% EtOAc/hexane); ^1H NMR (400 MHz, $CDCl_3$) δ

8.03 (1H, s, Ar**H**), 7.88-7.82 (3H, m, Ar**H** + =C**H**), 7.67-7.64 (2H, m, Ar**H**), 7.55-7.49 (2H, m, Ar**H**). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 136.9 (CH), 132.9 (2 x C), 132.7 (C), 128.2 (CH), 128.1 (CH), 128.0 (CH), 127.7 (CH), 126.7 (CH), 126.5 (CH), 125.6 (CH), 89.8 (C). NMR spectral data in agreement with literature.[117]



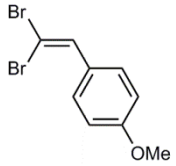
1-(2,2-Dibromo-vinyl)-4-fluoro-benzene (234b)

The title compound was prepared according to General Procedure A using 4-fluorobenaldehyde (5.40 mL, 50.0 mmol) and purified by column chromatography (10% EtOAc/hexane) to give a yellow oil (14.5 g, >99%). R_f = 0.79 (10% EtOAc/hexane); IR (film) 3047, 2674, 1603, 1508, 1413, 1265, 1231, 1160, 909, 739 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.50 (2H, m, Ar**H**), 7.45 (1H, s, =C**H**), 7.07 (2H, t, *J* = 8.7 Hz, Ar**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 162.4 (CF, d, *J* = 250.0 Hz), 135.7 (CH), 131.4 (C, d, *J* = 3.5 Hz), 130.3 (CH, d, *J* = 8.2 Hz), 115.5 (CH, d, *J* = 21.7), 89.6 (C, d, *J* = 2.3 Hz). NMR spectral data in agreement with literature.[118]



1-(2,2-Dibromo-vinyl)-3-nitro-benzene (234c)

The title compound was prepared according to General Procedure A using 3-nitrobenzaldehyde (6.04 g, 40.0 mmol) and purified by column chromatography (5% EtOAc/Hexane→15% EtOAc/hexane) to give a yellow solid (6.07 g, 49%). R_f = 0.45 (10% EtOAc/hexane); m.p. 54-56 °C; IR (solid) 3086, 1520 (N-O), 1473, 1352 (N-O), 903, 837, 802, 731 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (1H, t, *J* = 1.7 Hz, Ar**H**), 8.21 (1H, dd, *J* = 8.3, 1.4 Hz, Ar**H**), 7.84 (1H, d, *J* = 7.8 Hz, Ar**H**), 7.57 (1H, t, J = 8.1 Hz, Ar**H**), 7.55 (1H, s, =C**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 148.2 (C), 136.8 (C), 134.5 (CH), 134.2 (CH), 129.4 (CH), 123.2 (CH), 123.2 (CH), 93.3 (C).

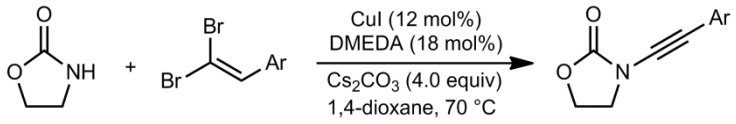


1-(2,2-Dibromo-vinyl)-4-methoxy-benzene (234d)

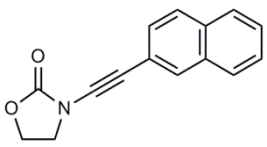
The title compound was prepared according to General Procedure A using 4-methoxybenaldehyde (6.06 mL, 50.0 mmol) and purified by column chromatography (10% EtOAc/hexane and then) to give a pale yellow solid (12.9 g, 88%). R_f = 0.59 (10% EtOAc/hexane); IR (film) 3004,

2957, 2931, 2835, 1605, 1508, 1461, 1305, 1178, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (2H, d, *J* = 8.8 Hz, Ar**H**), 7.42 (1H, s, =C**H**), 6.90 (2H, d, *J* = 8.8 Hz, Ar**H**), 3.83 (3H, s, OC**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 159.6 (C), 136.3 (CH), 129.9 (2 x CH), 127.8 (C), 113.8 (2 x CH), 87.3 (C), 55.3 (CH_3). NMR spectral data in agreement with literature.[117]

Preparation of Ynamides From Dibromoalkenes: General Procedure B

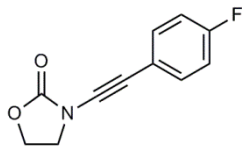


Following the procedure of Evano and co-workers,[10] to a suspension of 2-oxazolidinone (1.0 equiv), CuI (0.12 equiv), and Cs_2CO_3 (4.0 equiv) in 1,4-dioxane (2 mL/mmol of 2-oxazolidinone) was added the appropriate dibromoalkene (1.5 equiv) using 1,4-dioxane (10 mL). DMEDA (0.18 equiv) was added and the reaction mixture was heated at 70 °C for 24 h. The mixture was filtered through a pad of silica gel using EtOAc (100 mL) as eluent. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography to give the desired ynamide.



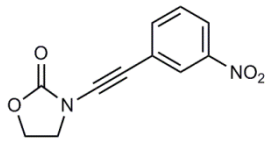
3-Naphthalen-2-ylethynyloxazolidin-2-one (83h)

The title compound was prepared according to General Procedure B using 2-oxazolidinone (1.80 g, 12.4 mmol) and dibromoalkene **232a** (5.80 g, 18.6 mmol) and purified by column chromatography (30% EtOAc/hexane→60% EtOAc/hexane) to give a pale yellow solid (1.11 g, 38%), which was recrystallised from chloroform to give a white crystalline solid (352 mg, 12%). R_f = 0.46 (60% EtOAc/hexane); m.p. 173-175 °C IR (film) 3052, 2986, 2252, 1755 (C=O), 1478, 1416, 1213, 1156, 738, 703 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 8.03 (1H, s, Ar**H**), 7.93-7.90 (3H, m, Ar**H**), 7.56-7.51 (2H, m, Ar**H**), 7.48 (1H, dd, *J* = 8.5, 1.4 Hz, Ar**H**), 4.49 (2H, dd, *J* = 8.3, 7.6 Hz, C**H**$_2$O), 4.05 (2H, dd, *J* = 8.2, 7.7 Hz, C**H**$_2$N); ^{13}C NMR (125.8 MHz, $(CD_3)_2SO$) δ 155.8 (C), 132.6 (C), 132.1 (C), 130.3 (CH), 128.2 (CH), 127.8 (CH), 127.6 (CH), 127.5 (CH), 126.7 (2 x CH), 119.2 (C) 81.0 (C), 70.3 (C), 63.7 (CH_2), 46.6 (CH_2); HRMS (ES) Exact mass calcd for $C_{15}H_{15}N_2O_2$ $[M+NH_4]^+$: 255.1128, found: 255.1132.



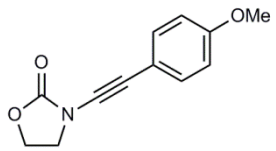
3-(4-Fluorophenylethynyl)oxazolidin-2-one (83i)

The title compound was prepared according to General Procedure B using 2-oxazolidinone (2.26 g, 26.0 mmol) and dibromoalkene **232b** (10.9 g, 39.0 mmol) and purified by column chromatography (5% EtOAc/hexane→60% EtOAc/hexane) to give a white solid (1.60 g, 30%). R_f = 0.39 (50% EtOAc/hexane); m.p. 112-114 °C; IR (film) 3054, 2986, 1775 (C=O), 1601, 1513, 1415, 1265, 1206, 740, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.41 (2H, m, Ar**H**), 7.04-6.99 (2H, m, Ar**H**), 4.52-4.49 (2H, m, C**H**$_2$O), 4.03-4.00 (2H, m, C**H**$_2$N); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 162.5 (C, d, *J* = 250.0 Hz), 155.9 (C), 133.7 (2 x CH, d, *J* = 8.4 Hz), 118.2 (C, d, *J* = 3.5 Hz) 115.6 (2 x CH, d, *J* = 22.0 Hz), 78.5 (C), 70.2 (C), 63.0 (CH_2), 47.0 (CH_2); ^{19}F NMR (376.3 MHz, $CDCl_3$) δ –111.0 (1F, tt, *J* = 8.6, 5.3 Hz); HRMS (ES) Exact mass calcd for $C_{11}H_{12}FN_2O_2$ $[M+NH_4]^+$: 223.0877, found: 223.0876.



3-(3-Nitrophenylethynyl)oxazolidin-2-one (83j)

The title compound was prepared according to General Procedure B using 2-oxazolidinone (1.10 g, 12.7 mmol) and dibromoalkene **232c** (5.83 g, 19.0 mmol). The residue was purified by column chromatography (30% EtOAc/hexane→50% EtOAc/hexane) to give a yellow solid (830 mg, 28%). R_f = 0.41 (60% EtOAc/Hexane); m.p. 114-116 °C; IR (film) 3055, 2986, 2926, 2263, 1780 (C=O), 1534 (N-O), 1409, 1353 (N-O), 1265, 739 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.26 (1H, t, *J* = 1.9 Hz, Ar**H**), 8.14 (1H, ddd, *J* = 8.3, 2.3, 1.0 Hz, Ar**H**), 7.73 (1H, dt, *J* = 7.7, 2.2 Hz, Ar**H**), 7.50 (1H, t, *J* = 8.0 Hz, Ar**H**), 4.56-4.53 (2H, m, C**H**$_2$O), 4.08-4.05 (2H, m, C**H**$_2$N); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 155.5 (C), 148.1 (C), 136.9 (CH), 129.3 (CH), 125.9 (CH), 124.2 (C), 122.7 (CH), 81.4 (C), 69.5 (C), 63.2 (CH_2), 46.8 (CH_2); HRMS (ES) Exact mass calcd for $C_{11}H_{12}N_3O_4$ $[M+NH_4]^+$: 250.0822, found: 250.0825.



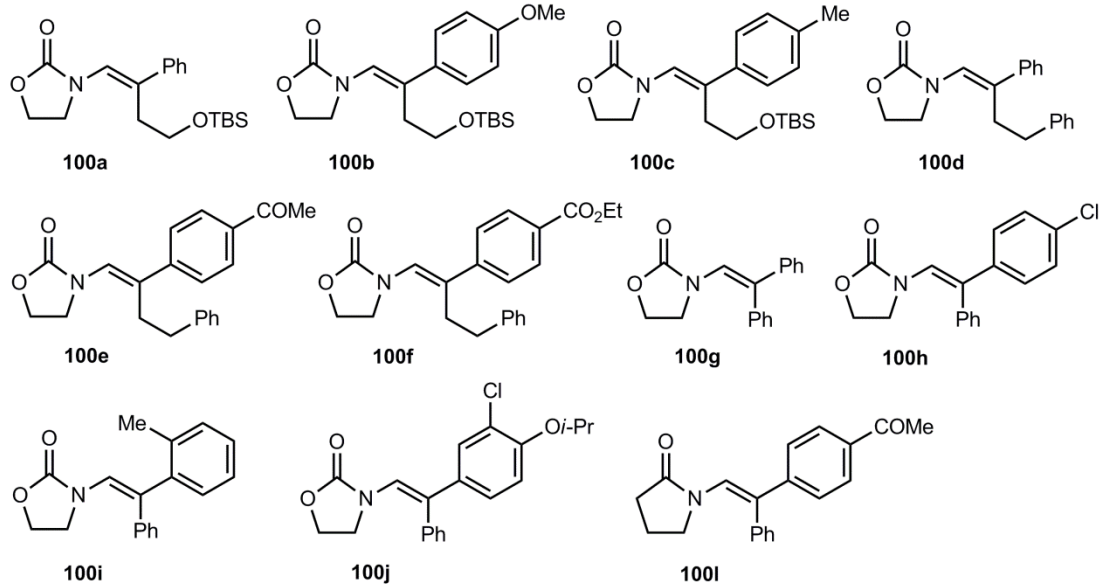
3-(4-Methoxyphenylethynyl) oxazolidin-2-one (83k)

The title compound was prepared according to General Procedure B using 2-oxazolidinone (1.22 g, 14.0 mmol) and dibromoalkene **232d** (6.12 g, 21.0 mmol). The residue was purified by column

chromatography (5% EtOAc/hexane→50% EtOAc/hexane) to give a yellow solid (1.61 mg, 53%). R_f = 0.24 (40% EtOAc/hexane); m.p. 93-95 °C; IR (film) 2962, 2920, 1745 (C=O), 1604, 1514, 1417, 1250, 1213, 1176, 823 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41-7.37 (2H, m, Ar**H**), 6.86-6.82 (2H, m, Ar**H**), 4.48 (2H, dd, *J* = 8.7, 7.3 Hz, C**H**$_2$O), 4.01-3.97 (2H, dd, *J* = 8.7, 7.3 Hz, C**H**$_2$N), 3.81 (3H, s, OC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 159.7 (C), 156.0 (C), 133.4 (2 x CH), 114.0 (C) 113.9 (2 x CH), 77.6 (C), 70.9 (C), 62.9 (CH_2), 55.2 (CH_3), 47.1 (CH_2). Spectral data in agreement with literature.[9,119]

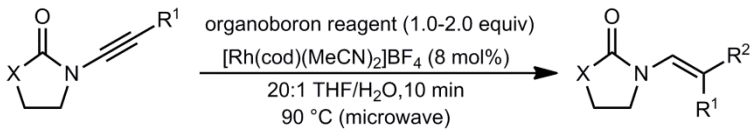
5.2 Chapter 2 Experimental

Carbometalation of Ynamides



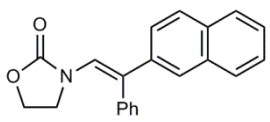
Enamides **100a-j** and **100l** were prepared by Lam group member Benoit Gourdet, as detailed in the published experimental procedure.[59]

Carbometalation of Ynamides: General Procedure C



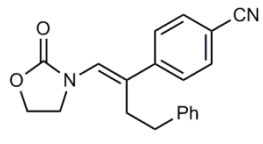
A solution of the appropriate ynamide (0.40 mmol), the organoboron reagent (1.0–2.0 equiv), and $[Rh(cod)(MeCN)_2]BF_4$ (12 mg, 0.032 mmol) in THF (2 mL) and H_2O

(100 μL) was heated at 90 °C for 10 min under microwave irradiation. Saturated aqueous $NaHCO_3$ solution (5 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography gave the desired enamide.



3-[(*E*)-2-Naphthalen-2-yl-2-phenylvinyl]oxazolidin-2-one (100k)

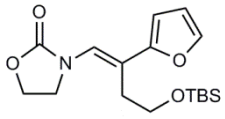
This enamide was synthesised by Benoit Gourdet. The title compound was prepared according to a slight modification of General Procedure C. A solution of ynamide **83a** (187 mg, 1.00 mmol), naphthalene-2-boronic acid (344 mg, 2.00 mmol), and $[Rh(cod)(MeCN)_2]BF_4$ (31 mg, 0.08 mmol) in THF (5 mL) and H_2O (250 μL) was heated at 90 °C for 10 min under microwave irradiation. Saturated aqueous $NaHCO_3$ solution (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/hexane→25% EtOAc/hexane) gave the *enamide* **100k** (161 mg, 51%) as a pale yellow solid. R_f = 0.51 (40% EtOAc/hexane); m.p. 110-112 °C; IR ($CHCl_3$) 2921, 2855, 1750 (C=O), 1641, 1596, 1443, 1280, 1210, 1041, 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.81-7.79 (1H, m, Ar**H**), 7.75-7.72 (2H, m, Ar**H**), 7.58 (1H, s, =C**H**), 7.46-7.39 (6H, m, Ar**H**), 7.33-7.31 (3H, m, Ar**H**), 4.24-4.20 (2H, m, C**H**$_2$O), 3.20-3.16 (2H, m, C**H**$_2$N); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 157.2 (C), 138.2 (C), 137.9 (C), 133.3 (C), 132.4 (C), 130.9 (2 × CH), 128.3 (2 × CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 127.5 (CH), 126.2 (CH), 125.9 (CH and C), 125.7 (CH), 125.1 (CH), 122.8 (CH), 62.6 (CH_2), 44.9 (CH_2); HRMS (ES) Exact mass calcd for $C_{21}H_{18}NO_2$ $[M+H]^+$: 316.1332, found: 316.1333.



3-[(*E*)-4-phenyl-2-(4-benzonitrile)but-1-enyl]oxazolidin-2-one (100m)

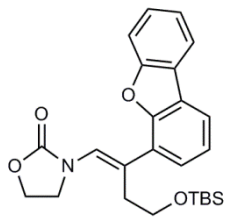
The title compound was prepared according to General Procedure C using ynamide **83c** (86 mg, 0.40 mmol) and 4-cyanophenylboronic acid (117mg, 0.80 mmol) and purified by column chromatography (15%

EtOAc/hexane→40% EtOAc/hexane) to give *enamide* **100m** (10mg, 9%) as a cream solid. R_f = 0.27 (50% EtOAc/hexane); m.p. 124-127 °C; IR (CH_2Cl_2) 3154, 2926, 1758 (C=O), 1648, 1603, 1404, 1216, 1090, 907, 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.66 (2H, d, *J* = 8.4 Hz, Ar**H**), 7.49 (2H, d, *J* = 8.4 Hz, Ar**H**), 7.29 (2H, app t, *J* = 7.2 Hz, Ar**H**), 7.21 (1H, t, *J* = 7.3 Hz, Ar**H**), 7.10 (2H, d, *J* = 7.0 Hz, Ar**H**), 6.58 (1H, s, =C**H**), 4.37-4.33 (2H, m, C$\mathbf{H}_2$O), 3.69-3.65 (2H, m, C$\mathbf{H}_2$N), 2.90 (2H, t, *J* = 7.5 Hz, C$\mathbf{H}_2$Ph), 2.68 (2H, t, *J* =7.5 Hz, C$\mathbf{H}_2$$CH_2$Ph); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 156.8 (C), 145.4 (C), 140.7 (C), 132.4 (2 x CH), 128.5 (2 x CH), 128.4 (2 x CH), 127.3 (2 x CH), 126.8 (C), 126.4 (CH), 125.1 (CH), 118.8 (C), 110.7 (C), 62.3 (CH_2), 45.6 (CH_2), 34.4 (CH_2), 30.9 (CH_2); HRMS (ES) Exact mass calcd for $C_{20}H_{22}N_3O_2$ $[M+NH_4]^+$: 336.1707, found: 336.1705.



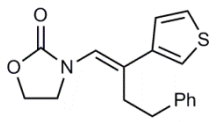
3-[(*E*)-4-(*tert*-Butyldimethylsilyloxy)-2-(2-furanyl)but-1-enyl]oxazolidin-2-one (100n)

The title compound was prepared according to General Procedure C using ynamide **83b** (108 mg, 0.40 mmol) and 2-furanboronic acid (90 mg, 0.80 mmol) and purified by column chromatography (10% EtOAc/hexane→20% EtOAc/hexane) to give *enamide* **100n** (89 mg, 66%) as a cream solid. R_f = 0.67 (50% EtOAc/hexane); m.p. 54-56 °C; IR (CH_2Cl_2) 3055, 2986, 2957, 2930, 2857, 1759 (C=O), 1654, 1550, 1421, 1403, 1265, 1226, 1082, 896, 837, 739, 705 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 (1H, d, *J* = 1.8 Hz, Ar**H**), 7.17 (1H, s, =C**H**), 6.37 (1H, dd, *J* = 3.3, 1.8 Hz, Ar**H**), 6.20 (1H, d, *J* = 3.3 Hz, Ar**H**), 4.45-4.41 (2H, m, C$\mathbf{H}_2$O), 4.20-4.16 (2H, m, C$\mathbf{H}_2$N), 3.75 (2H, t, *J* = 6.5 Hz, C$\mathbf{H}_2$OSi), 2.71 (2H, t, *J* = 6.5 Hz, =CC$\mathbf{H}_2$), 0.86 (9H, s, SiC(C$\mathbf{H}_3$)$_3$), –0.02 (6H, s, Si(C$\mathbf{H}_3$)$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 156.9 (C), 154.2 (C), 141.3 (CH), 121.9 (CH), 112.6 (C), 111.1 (CH), 104.7 (CH), 62.4 (CH_2), 61.9 (CH_2), 45.6 (CH_2), 30.5 (CH_2), 25.8 (3 x CH_3), 18.3 (C), –5.5 (2 x CH_3); HRMS (ES) Exact mass calcd for $C_{17}H_{28}NO_4Si$ $[M+H]^+$: 338.1778, found: 338.1782.



3-[(*E*)-4-(*tert*-Butyldimethylsilyloxy)-2-(4-dibenzofuranyl)but-1-enyl]oxazolidin-2-one (100o)

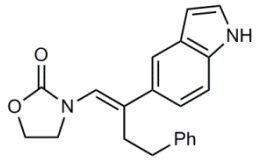
The title compound was prepared according to General Procedure C using ynamide **83b** (108 mg, 0.40 mmol) and 4-dibenzofuranboronic acid (169 mg, 0.80 mmol) and purified by column chromatography (10% EtOAc/hexane→20% EtOAc/hexane) to give a 13:1 inseparable mixture of the *enamide* **100o** and the imide **102** as a cream solid (84 mg, 46%, adjusted yield of **100o**). Data for **100o**: R_f = 0.49 (50% EtOAc/hexane); m.p. 88-91 °C; IR (CH_2Cl_2) 3055, 2954, 2928, 2857, 1759 (C=O), 1655, 1583, 1472, 1451, 1404, 1264, 1226, 1187, 1090, 837, 750, 704 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.96 (1H, dd, *J* = 7.6, 0.6 Hz, Ar**H**), 7.88 (1H, dd, *J* = 7.5, 1.4 Hz, Ar**H**), 7.57 (1H, d, *J* = 8.2 Hz, Ar**H**), 7.48-7.45 (1H, m, Ar**H**), 7.38-7.34 (2H, m, Ar**H**), 7.31 (1H, t, *J* = 7.6 Hz, Ar**H**), 6.91 (1H, s, =C**H**), 4.51-4.47 (2H, m, C$\mathbf{H}_2$O), 4.30-4.26 (2H, m, C$\mathbf{H}_2$N), 3.62 (2H, t, *J* = 6.4 Hz, C$\mathbf{H}_2$OSi), 3.11 (2H, t, *J* = 6.4 Hz, =CC$\mathbf{H}_2$), 0.84 (9H, s, SiC(C$\mathbf{H}_3$)$_3$), –0.08 (6H, s, Si(C$\mathbf{H}_3$)$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 157.2 (C), 155.8 (C), 153.6 (C), 127.3 (CH), 127.1 (CH), 128.1 (CH), 125.7 (CH), 124.4 (CH), 124.1 (CH), 122.9 (CH), 122.7 (CH), 120.9 (CH), 120.6 (CH), 119.5 (CH), 111.7 (CH), 62.5 (CH_2), 61.2 (CH_2), 46.1 (CH_2), 32.6 (CH_2), 25.8 (3 x CH_3), 18.2 (C), –5.6 (2 x CH_3); HRMS (ES) Exact mass calcd for $C_{25}H_{32}NO_4Si$ $[M+H]^+$: 438.2091, found: 438.2095.



3-[(*E*)-4-phenyl-2-(3-thiophenyl)but-1-enyl]oxazolidin-2-one (100p)

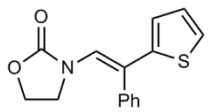
The title compound was prepared according to General Procedure C but without the addition of H_2O to the reaction mixture. Ynamide **83c** (86 mg, 0.40 mmol) and 3-thiopheneboronic acid (102 mg, 0.80 mmol) were used and the residue purified by column chromatography (15% EtOAc/hexane→20% EtOAc/hexane) to give the *enamide* **100p** (45 mg, 37%) as a cream solid. R_f = 0.57 (60% EtOAc/hexane); m.p. 81-84 °C; IR (CH_2Cl_2) 3103, 3024, 2921, 1754 (C=O), 1648, 1478, 1400, 1220, 1085, 753 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35-7.33 (1H, dd, *J* = 5.0, 3.0 Hz, Ar**H**), 7.30 (2H, t, *J* = 7.4 Hz, Ar**H**), 7.24-7.19 (3H, m, Ar**H**), 7.17-7.15 (2H, m, Ar**H**), 6.58 (1H, s, =C**H**), 4.31-4.28 (2H, m, C$\mathbf{H}_2$O), 3.57-3.53 (2H, m,

C**H**$_2$N), 2.85-2.78 (4H, m, C**H**$_2$C**H**$_2$Ph); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 157.0 (C), 141.4 (C), 141.1 (C), 128.5 (2 x CH), 128.4 (2 x CH), 126.2 (CH), 126.0 (CH), 126.0 (C), 125.7 (CH), 121.7 (CH), 120.2 (CH), 62.2 (CH_2), 46.0 (CH_2), 34.7 (CH_2), 31.7 (CH_2); HRMS (ES) Exact mass calcd for $C_{17}H_{18}NO_2S$ $[M+H]^+$: 300.1053, found: 300.1055.



3-[(*E*)-2-(1*H*-Indol-5-yl)-4-phenyl-but-1-enyl]-oxazolidin-2-one (100q)

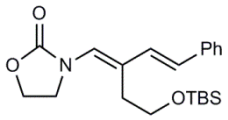
The title compound was prepared according to General Procedure C using ynamide **83c** (86 mg, 0.40 mmol) and indole-5-boronic acid (129 mg, 0.80 mmol) and purified by column chromatography (25% EtOAc/hexane→50% EtOAc/hexane) to give 9:1 inseparable mixture of *enamide* **100q** and its regioisomer as a brown oil (44 mg, 30%, adjusted yield of **100q**). Data for **100q**: R_f = 0.21 (50% EtOAc/hexane); IR (CH_2Cl_2) 3054, 2987, 1752 (C=O), 1422, 1265, 896, 738, 705 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (1H, s, N**H**), 7.70-7.69 (1H, m, Ar**H**), 7.40 (1H, d, J = 8.5 Hz, Ar**H**), 7.30-7.24 (4H, m, Ar**H**), 7.21-7.15 (3H, m, Ar**H**), 6.58-6.59 (1H, m, Ar**H**), 6.33 (1H, s, =C**H**), 4.33-4.29 (2H, m, C**H**$_2$O), 3.57-3.53 (2H, m, C**H**$_2$N), 2.94 (2H, t, J= 7.7 Hz, C**H**$_2$Ph), 2.72 (2H, t, J = 7.7 Hz, C**H**$_2$CH$_2$Ph); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 157.3 (C), 141.9 (C), 135.4 (C), 134.5, 131.7, 128.6 (2 x CH), 128.3 (2 x CH), 128.0, 126.0 (CH), 124.7 (CH), 121.5 (C), 121.3 (CH), 119.2 (CH), 111.0, 102.9, 62.2 (CH_2), 46.4 (CH_2), 34.3 (CH_2), 32.2 (CH_2); HRMS (ES) Exact mass calcd for $C_{21}H_{21}N_2O_2$ $[M+H]^+$: 333.1598, found: 333.1601.



3-[(*E*)-2-Phenyl-2-thiophen-2-ylvinyl]oxazolidin-2-one (100r)

This enamide was synthesised by Benoit Gourdet. The title compound was prepared according to a slight modification of General Procedure C. A solution of ynamide **83a** (374 mg, 2.00 mmol), thiophene-2-boronic acid (511 mg, 4.00 mmol), and $[Rh(cod)(MeCN)_2]BF_4$ (60 mg, 0.16 mmol) in THF (10 mL) and H_2O (500 μL) was heated at 90 °C for 10 min under microwave irradiation. Saturated aqueous $NaHCO_3$ solution (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the residue by column

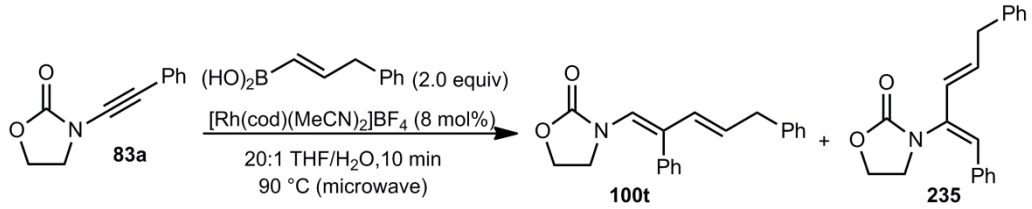
chromatography (10% EtOAc/hexane→20% EtOAc/hexane) gave the *enamide* **100r** (207 mg, 38%) as a pale yellow solid. R_f = 0.49 (40% EtOAc/hexane); m.p. 83-85 °C; IR (film) 2985, 2916, 1757 (C=O), 1638, 1516, 1478, 1400, 1261, 910, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42-7.38 (3H, m, Ar**H**), 7.36-7.34 (2H, m, Ar**H**), 7.25 (1H, s, =C**H**), 7.13 (1H, dd, *J* = 5.1, 1.0 Hz, Ar**H**), 6.90 (2H, dd, *J* = 5.1, 3.6 Hz, Ar**H**), 6.63 (1H, dd, *J* = 3.6, 1.0 Hz, Ar**H**), 4.20-4.17 (2H, m, C$\mathbf{H}_2$O), 3.12-3.09 (2H, m, C$\mathbf{H}_2$N); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 156.8 (C), 145.4 (C), 137.3 (C), 130.6 (2 × CH), 128.3 (CH), 128.2 (2 × CH), 127.3 (CH), 124.6 (CH), 123.8 (CH), 121.2 (CH), 120.5 (C), 62.5 (CH_2), 44.8 (CH_2); HRMS (ES) Exact mass calcd for $C_{15}H_{14}NO_2S$ $[M+H]^+$: 272.0740, found: 272.0733.



3-{(1E,3E)-2-[2-(tert-Butyldimethylsilyloxy)ethyl]-4-phenylbuta-1,3-dienyl}-oxazolidin-2-one (100s)

This enamide was synthesised by Benoit Gourdet. The title compound was prepared according to General Procedure C using ynamide **83b** (108 mg, 0.40 mmol) and *trans*-2-phenylvinylboronic acid (118 mg, 0.8 mmol) and purified by column chromatography (10% EtOAc/hexane) to give the *enamide* **100s** (78 mg, 52%) as a pale brown solid. R_f = 0.80 (60% EtOAc/hexane); m.p. = 130-132 °C; IR (film) 2925, 1731 (C=O), 1635, 1461, 1406, 1337, 1250, 1224, 1044, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39-7.37 (2H, m, Ar**H**), 7.33-7.30 (2H, m, Ar**H**), 7.22-7.19 (1H, m, Ar**H**), 6.77 (1H, s, =C**H**), 6.75 (1H, d, *J* = 16.1 Hz, C**H**=CH), 6.45 (1H, d, *J* = 16.1 Hz, CH=C**H**), 4.41 (2H, app dd, *J* = 9.2, 6.9 Hz, C$\mathbf{H}_2$O), 4.21 (2H, app dd, *J* = 9.2, 6.9 Hz, C$\mathbf{H}_2$N), 3.77 (2H, t, *J* = 6.4 Hz, C$\mathbf{H}_2$OSi), 2.70 (2H, t, *J* = 6.4 Hz, =CC$\mathbf{H}_2$), 0.87 (9H, s, SiC(C$\mathbf{H}_3$)$_3$), 0.02 (6H, s, Si(C$\mathbf{H}_3$)$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 156.7 (C), 137.6 (C), 130.9 (CH), 128.6 (2 × CH), 127.4 (CH), 127.0 (CH), 126.0 (2 × CH), 125.1 (CH), 120.1 (C), 62.3 (CH_2), 61.6 (CH_2), 45.5 (CH_2), 29.0 (CH_2), 25.8 (3 × CH_3), 18.3 (C), –5.4 (2 × CH_3); HRMS (ES) Exact mass calcd for $C_{21}H_{32}NO_3Si$ $[M+H]^+$: 374.2146, found: 374.2136.

3-((1*Z*,3*E*)-2,5-diphenylpenta-1,3-dienyl)-oxazolidin-2-one (100t)



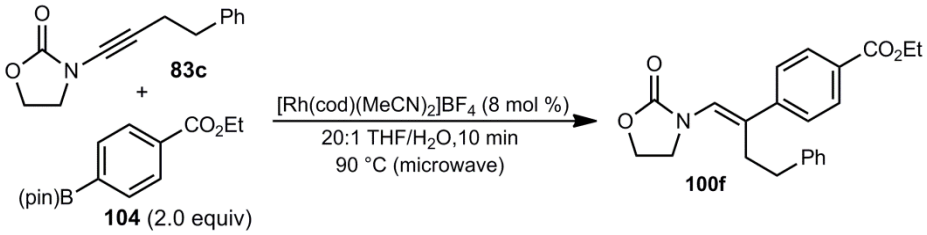
This reaction was performed by Benoit Gourdet. The title compounds were prepared according to General Procedure C using *trans*-3-phenyl-1-propen-1-ylboronic acid (130 mg, 0.8 mmol) and ynamide **83a** (75 mg, 0.40 mmol) and purified by column chromatography (15% EtOAc/hexane) to give the *enamide* **100t** (45 mg, 37%) as a pale brown followed by the regioisomeric *enamide* **235** (42 mg, 18%) as an orange solid.

Data for **100t**: R_f = 0.79 (60% EtOAc/hexane); mp = 84-86 °C; IR (film) 3025, 2915, 1758 (C=O), 1641, 1479, 1403, 1329, 1243, 1037, 753 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.31 (3H, m, Ar**H**), 7.29-7.26 (2H, m, Ar**H**), 7.23-7.17 (3H, m, Ar**H**), 7.13-7.11 (2H, m, Ar**H**), 6.78 (1H, s, =C**H**), 6.29 (1H, d, *J* = 15.3 Hz, C**H**=CHCH$_2$), 5.25 (1H, dt, *J* = 15.3, 6.8 Hz, CH=C**H**CH$_2$), 4.13-4.10 (2H, m, C**H**$_2$O), 3.39 (2H, d, *J* = 6.8 Hz, CH=CHC**H**$_2$), 3.03-3.00 (2H, m, C**H**$_2$N); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.6 (C), 140.2 (C), 136.1 (C), 133.5 (CH), 130.5 (2 × CH), 129.5 (CH), 128.5 (2 × CH), 128.3 (2 × CH), 128.0 (2 × CH), 127.6 (CH), 126.0 (CH), 124.8 (C), 123.8 (CH), 62.4 (CH$_2$), 44.8 (CH$_2$), 38.9 (CH$_2$); HRMS (ES) Exact mass calcd for $C_{20}H_{20}NO_2$ $[M+H]^+$: 306.1494, found: 324.1485.

Data for **235**: R_f = 0.73 (60% EtOAc/hexane); IR (film) 3028, 2921, 1753 (C=O), 1601, 1495, 1415, 1246, 1077, 1043, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.21 (10H, m, Ar**H**), 6.53 (1H, s, =C**H**), 6.13 (1H, d, *J* = 15.4 Hz, C**H**=CHCH$_2$), 5.95 (1H, dt, *J* = 15.4, 6.8 Hz, CH=C**H**CH$_2$), 4.41-4.37 (2H, m, C**H**$_2$O), 3.59-3.54 (4H, m,CH=CHC**H**$_2$ + C**H**$_2$N); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.8 (C), 139.5 (C), 134.6 (C), 133.4 (CH), 130.6 (CH), 129.6 (CH), 128.7 (2 × CH), 128.5 (2 × CH), 128.4 (CH), 128.0 (2 × CH), 128.2 (CH), 126.3 (CH), 126.2 (C), 123.8 (CH), 62.4 (CH$_2$), 44.8 (CH$_2$), 38.9 (CH$_2$); HRMS (ES) Exact mass calcd for $C_{20}H_{20}NO_2$ $[M+H]^+$: 306.1489, found: 306.1486.

With arylboronic ester

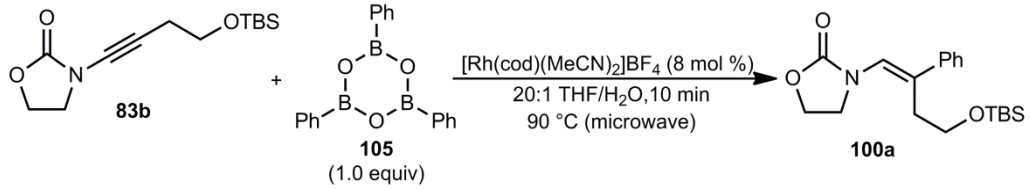
4-{1-[1-(2-Oxazolidin-3-yl)meth-(*E*)-ylidene]-3-phenylpropyl}benzoic acid ethyl ester (100f)



This reaction was performed by Benoit Gourdet. The title compound was prepared according to the General Procedure C using ynamide **83c** (86 mg, 0.40 mmol) and ethyl-4-(4,4,5,5)-tetramethyl-1,3,2,dioxaborolan-2-yl)benzoate (**104**) (220 mg, 0.80 mmol) and purified by column chromatography (10% EtOAc/hexane→20% EtOAc/hexane) to give the *enamide* **100f** (77 mg, 53%) as a pale yellow oil.

With boroxine reagent

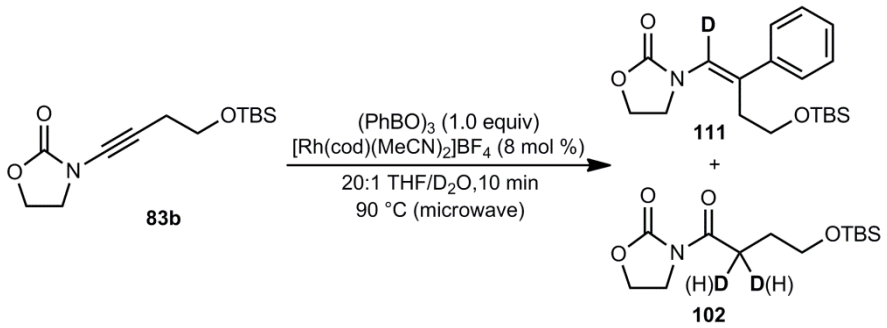
3-[(*E*)-4-(tert-Butyldimethylsilyloxy)-2-phenyl)but-1-enyl]oxazolidin-2-one (100a)



This reaction was performed by Benoit Gourdet. The title compound was prepared according to the General Procedure C using ynamide **83b** (108 mg, 0.40 mmol) and triphenylboroxine (**105**) (124 mg, 0.40 mmol) and purified by column chromatography (10% EtOAc/hexane→15% EtOAc/hexane) to give the *enamide* **100a** (81 mg, 58%) as a pale orange oil.

Deuterium incorporation experiment

3-[(*E*)-4-(tert-Butyldimethylsilyloxy)-1-deuterio-2-phenyl)but-1-enyl]oxazolidin-2-one (111)

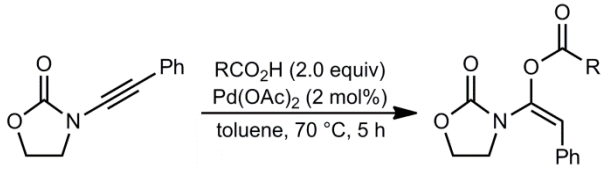


This reaction was performed by Benoit Gourdet. A solution of ynamide **83b** (108 mg, 0.40 mmol), triphenylboroxine (124 mg, 0.40 mmol), and $[Rh(cod)(MeCN)_2]BF_4$ (12 mg, 0.032 mmol) in THF (2 mL) and D_2O (100 μL) was heated at 90 °C for 10 min under microwave irradiation. Saturated aqueous $NaHCO_3$ solution (5 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the residue by column chromatography (10% EtOAc/hexane→15% EtOAc/hexane) gave a ca. 5:1 inseparable mixture of the *enamide* **111** and the imide **102** (mixture of isotopologues) as a pale orange oil (96 mg, 59%, adjusted yield of **111**).

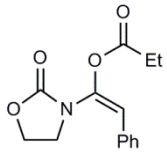
Data for **111**: R_f = 0.80 (60% EtOAc/hexane); IR (film) 2929, 2857, 1753 (C=O), 1639, 1598, 1471, 1297, 1255, 1051, 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34-7.30 (4H, m, Ar**H**), 7.27-7.24 (1H, m, Ar**H**), 4.43 (2H, app dd, J = 8.8, 7.1 Hz, C**H**$_2$O), 4.14 (2H, app dd, J = 9.0, 6.9 Hz, C**H**$_2$N), 3.60 (2H, t, J = 6.5 Hz, C**H**$_2$OSi), 2.83 (2H, t, J = 6.5 Hz, =CC**H**$_2$), 0.84 (9H, s, SiC(C**H**$_3$)$_3$), –0.06 (6H, s, Si(C**H**$_3$)$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 157.3 (C), 140.6 (C), 128.3 (2 × CH), 127.1 (CH), 126.8 (2 × CH), 125.6 (C), 123.5 (CD, t, J_D = 26 Hz), 62.4 (CH_2), 61.1 (CH_2), 46.1 (CH_2), 32.6 (CH_2), 25.8 (3 × CH_3), 18.2 (C), –5.5 (2 × CH_3); HRMS (ES) Exact mass calcd for $C_{19}H_{26}DNO_3Si$ $[M+H]^+$: 349.2052, found: 349.2050.

5.3 Chapter 3 Experimental

Hydroacyloxylation of Ynamide 83a: General Procedure D



A solution of ynamide **83a** (75 mg, 0.40 mmol), the appropriate carboxylic acid (0.80 mmol), and $Pd(OAc)_2$ (1.8 mg, 0.008 mmol) in toluene (4 mL) was heated at 70 °C in a sealed tube for 5 h. After cooling to room temperature, saturated aqueous $NaHCO_3$ solution (15 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography gave the desired α-acyloxyenamide.

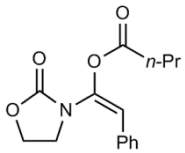


Propionic acid (*E*)-1-(2-oxo-oxazolidin-3-yl)-2-phenylvinyl ester (143b).

On a 0.40 mmol scale: The title compound was prepared according to General Procedure D using propionic acid (60 μL, 0.80 mmol) and purified by column chromatography (50% EtOAc/hexane) to give a colourless oil (80 mg, 76%). R_f = 0.54 (50% EtOAc/hexane); IR (film) 3059, 2986, 2920, 1768 (C=O), 1675, 1481, 1448, 1399, 1226, 1108 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39-7.35 (2H, m, Ar**H**), 7.34-7.28 (3H, m, Ar**H**), 6.24 (1H, s, =C**H**), 4.37-4.33 (2H, m, C**H**$_2$O), 3.72-3.68 (2H, m, C**H**$_2$N), 2.56 (2H, q, *J* = 7.5 Hz, C**H**$_2$CH$_3$), 1.23 (3H, t, *J* = 7.5 Hz, C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 173.0 (C), 155.6 (C), 137.6 (C), 132.0 (C), 128.7 (2 x CH), 128.1 (3 x CH), 115.4 (CH), 63.1 (CH_2), 44.5 (CH_2), 27.1 (CH_2), 8.8 (CH_3); HRMS (ES) Exact mass calcd for $C_{14}H_{16}NO_4$ $[M+H]^+$: 262.1074, found: 262.1075.

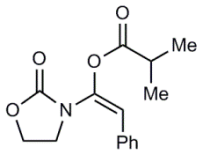
On a 3.0 mmol scale: A solution of ynamide **83a** (562 mg, 3.00 mmol), propionic acid (246 μL, 3.30 mmol), and $Pd(OAc)_2$ (6.7 mg, 0.03 mmol) in toluene (30 mL) was heated at 70 °C for 18 h. Saturated aqueous $NaHCO_3$ solution (50 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification

of the residue by column chromatography (15% EtOAc/hexane→30% EtOAc/hexane) gave the α-acyloxyenamide **143b** as a colorless oil (620 mg, 79%).



Butyric acid (*E*)-1-(2-oxo-oxazolidin-3-yl)-2-phenylvinyl ester (143c)

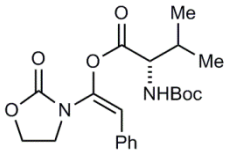
The title compound was prepared according to General Procedure D using butyric acid (73 μL, 0.80 mmol) and purified by column chromatography (50% EtOAc/hexane) to give a brown oil (96 mg, 87%). R_f = 0.54 (50% EtOAc/hexane); IR (film) 2966, 2934, 2877, 1770 (C=O), 1675, 1448, 1399, 1226, 1108, 1037 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39-7.28 (5H, m, Ar**H**), 6.24 (1H, s, =C**H**), 4.37-4.32 (2H, m, C**H**$_2$O), 3.72-3.67 (2H, m, C**H**$_2$N), 2.50 (2H, t, *J* = 7.4 Hz, C**H**$_2$CH$_2$CH$_3$), 1.75 (2H, sextet, *J* = 7.4 Hz, C**H**$_2$CH$_3$) 1.02 (3H, t, *J* = 7.4 Hz, C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 172.1 (C), 155.5 (C), 137.5 (C), 132.0 (C), 128.7 (2 x CH), 128.0 (3 x CH), 115.4 (CH), 63.1 (CH_2), 44.4 (CH_2), 35.5 (CH_2), 18.1 (CH_2), 13.5 (CH_3); HRMS (ES) Exact mass calcd for $C_{15}H_{18}NO_4$ $[M+H]^+$: 276.1230, found: 276.1232.



Isobutyric acid (*E*)-1-(2-oxo-oxazolidin-3-yl)-2-phenylvinyl ester (143d)

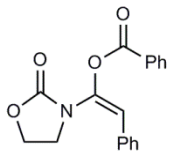
Using 2.0 equiv of carboxylic acid: The title compound was prepared according to General Procedure D using isobutyric acid (74 μL, 0.80 mmol) and purified by column chromatography (20% EtOAc/hexane→25% EtOAc/hexane) to give a cream solid (95 mg, 86%). R_f = 0.61 (50% EtOAc/hexane); m.p. 62-64 °C; IR (film) 3057, 2981, 1768 (C=O), 1676, 1401, 1265, 1224, 1111, 1089, 735; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40-7.28 (5H, m, Ar**H**), 6.25 (1H, s, =C**H**), 4.37-4.34 (2H, m, C**H**$_2$O), 3.72-3.69 (2H, m, C**H**$_2$N), 2.78 (1H, septet, *J* = 7.0 Hz, C**H**$(CH_3)_2$), 1.30 (6H, d, *J* = 7.0 Hz, CH(C**H**$_3)_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 175.7 (C), 155.5 (C), 137.7 (C), 132.0 (C), 128.7 (2 x CH), 128.0 (3 x CH), 115.3 (CH), 63.1 (CH_2), 44.5 (CH_2), 33.8 (CH), 18.7 (2 x CH_3); HRMS (ES) Exact mass calcd for $C_{15}H_{21}N_2O_4$ $[M+NH_4]^+$: 293.1496, found: 293.1496.

Using 1.1 equiv of carboxylic acid: A repeat of the above reaction using isobutyric acid (41 μL, 0.44 mmol) under otherwise identical conditions gave the title compound (93 mg, 84%) as a cream solid.



(*E*)-1-(2-Oxo-1,3-oxazolidin-3-yl)-2-phenylethenyl 2-{[(*tert*-butoxy)carbonyl]amino}-3-methylbutanoate (143e)

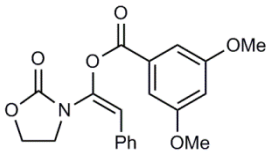
The title compound was prepared according to General Procedure D using L-Boc-valine-OH (174 mg, 0.80 mmol) and purified by column chromatography (20% EtOAc/hexane→25% EtOAc/hexane) to give an orange gum (173 mg, >95%). R_f = 0.54 (50% EtOAc/hexane); $[\alpha]_D^{20}$ +15.5 (*c* 1.04 $CHCl_3$); IR (film) 3056, 2987, 2921, 1774 (C=O), 1676, 1532, 1353, 1266, 1111, 737 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38-7.28 (5H, m, Ar**H**), 6.30 (1H, s, =C**H**), 5.00 (1H, br d, *J* = 8.6 Hz, N**H**), 4.37-4.33 (3H, m, C**H**N and C$\mathbf{H}_2$O), 3.78-3.68 (2H, m, C$\mathbf{H}_2$N), 2.35-2.29 (1H, m, C**H**$(CH_3)_2$), 1.48 (9H, s, C$(C\mathbf{H}_3)_3$), 1.06 (3H, d, *J* = 6.9 Hz, CH$(C\mathbf{H}_3)_2$), 0.98 (3H, d, *J* = 6.9 Hz, CH$(C\mathbf{H}_3)_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 171.2 (C), 155.7 (C), 155.4 (C), 137.0 (C), 131.7 (C), 128.8 (2 x CH), 128.3 (CH), 128.1 (2 x CH), 117.0 (CH), 80.1 (C), 63.2 (CH_2), 58.7 (CH), 44.3 (CH_2), 30.7 (CH), 28.3 (3 x CH_3), 19.3 (CH_3), 17.4 (CH_3); HRMS (ES) Exact mass calcd for $C_{21}H_{32}N_3O_6$ $[M+NH_4]^+$: 422.2286, found: 422.2283.



Benzoic acid (*E*)-1-(2-oxo-oxazolidin-3-yl)-2-phenylvinyl ester (143f)

The title compound was prepared according to General Procedure D using benzoic acid (98 mg, 0.80 mmol) and purified by column chromatography (20% EtOAc/hexane) to give a pale orange gum (124 mg, >95%). R_f = 0.59 (50% EtOAc/hexane); IR (film) 3062, 3019, 2916, 1767 (C=O), 1739 (C=O), 1675, 1449, 1399, 1264, 1225 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.16 (2H, app dd, *J* = 8.4, 1.3 Hz, Ar**H**), 7.65 (1H, app tt, *J* = 7.5, 1.3 Hz, Ar**H**), 7.53-7.49 (2H, m, Ar**H**), 7.42-7.37 (4H, m, Ar**H**), 7.35-7.30 (1H, m, Ar**H**), 6.42 (1H, s, =C**H**), 4.40-4.36 (2H, m, C$\mathbf{H}_2$O), 3.83-3.79 (2H, m, C$\mathbf{H}_2$N); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 165.3 (C), 155.6 (C), 137.6 (C), 134.0 (CH), 132.0 (C), 130.4 (2 x CH), 128.8 (2 x CH), 128.7 (2 x

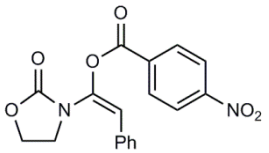
CH), 128.4 (C), 128.2 (CH), 128.1 (2 x CH), 116.5 (CH), 63.2 (CH_2), 44.5 (CH_2); HRMS (ES) Exact mass calcd for $C_{18}H_{16}NO_4$ $[M+H]^+$: 310.1074, found: 310.1074.



3,5-Dimethoxybenzoic acid (*E*)-1-(2-oxo-oxazolidin-3-yl)-2-phenylvinyl ester (143g)

Using 2.0 equiv of carboxylic acid: The title compound was prepared according to General Procedure D using 3,5-dimethoxybenzoic acid (146 mg, 0.80 mmol) and purified by column chromatography (50% EtOAc/hexane) to give a light brown oil (123 mg, 83%). R_f = 0.44 (50% EtOAc/hexane); IR (film) 3058, 2963, 2938, 2841, 1767 (C=O), 1735 (C=O), 1677, 1595, 1205, 1040 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41-7.38 (4H, m, Ar**H**), 7.34-7.31 (1H, m, Ar**H**), 7.30 (2H, d, *J* = 2.4 Hz, Ar**H**), 6.73 (1H, t, *J* = 2.4 Hz, Ar**H**), 6.41 (1H, s, =C**H**), 4.39-4.36 (2H, m, C$\mathbf{H}_2$O), 3.86 (6H, s, 2 x OC$\mathbf{H}_3$), 3.82-3.78 (2H, m, C$\mathbf{H}_2$N); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 165.0 (C), 160.8 (2 x C), 155.5 (C), 137.5 (C), 131.9 (CH), 130.1 (C), 128.8 (2 x CH), 128.2 (CH), 128.1 (2 x CH), 116.6 (CH), 107.7 (2 x CH), 106.0 (CH), 63.1 (CH_2), 55.6 (2 x CH_3), 44.5 (CH_2); HRMS (ASAP) Exact mass calcd for $C_{20}H_{20}NO_6$ $[M+H]^+$: 370.1285, found: 370.1289.

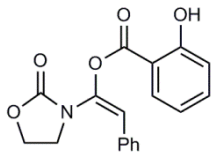
Using 1.1 equiv of carboxylic acid: A repeat of the above reaction using 3,5-dimethoxybenzoic acid (80 mg, 0.44 mmol) under otherwise identical conditions gave the title compound (132 mg, 89%) as a colorless oil.



4-Nitrobenzoic acid (*E*)-1-(2-oxo-oxazolidin-3-yl)-2-phenylvinyl ester (143h)

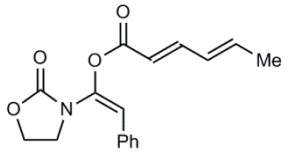
The title compound was prepared according to General Procedure D using 4-nitrobenzoic acid (134 mg, 0.80 mmol) and purified by column chromatography (25% EtOAc/hexane→35% EtOAc/hexane) to give a pale yellow solid (99 mg, 70%). R_f = 0.50 (50% EtOAc/hexane); m.p. 142-144 °C; IR (film) 2923, 2876, 1766 (C=O), 1677, 1527 (N-O), 1399, 1263, 1224, 1069 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.34 (4H, br s, Ar**H**), 7.43-7.36 (4H, m, Ar**H**), 7.36-7.31 (1H, m, Ar**H**), 6.43 (1H, s, =C**H**), 4.42-4.38 (2H, m, C$\mathbf{H}_2$O), 3.81-3.77 (2H, m, C$\mathbf{H}_2$N); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 163.3 (C), 155.5 (C), 151.0 (C), 137.4 (C), 133.8 (C), 131.54 (C), 131.47 (2 x CH), 128.9 (2 x CH), 128.4 (CH), 128.1 (2 x CH), 123.7

(2 x CH), 116.4 (CH), 63.2 (CH_2), 44.5 (CH_2); HRMS (ES) Exact mass calcd for $C_{18}H_{18}N_3O_6$ $[M+NH_4]^+$: 372.1190, found: 372.1193.



2-Hydroxybenzoic acid (*E*)-1-(2-oxo-oxazolidin-3-yl)-2-phenylvinyl ester (143i)

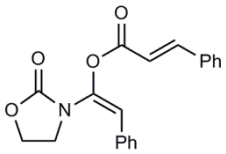
The title compound was prepared according to General Procedure D using salicylic acid (111 mg, 0.80 mmol) and purified by column chromatography (15% EtOAc/hexane→20% EtOAc/hexane) to give a colorless oil (98 mg, 75%). R_f = 0.69 (60% EtOAc/hexane); IR (film) 3253 (OH, br), 3058, 3026, 2917, 1770 (C=O), 1691 (C=O), 1614, 1483, 1401, 1205 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.24 (1H, s, O**H**), 8.03 (1H, dd, *J* = 8.0, 1.5 Hz, Ar**H**), 7.56-7.52 (1H, m, Ar**H**), 7.42-7.36 (4H, m, Ar**H**), 7.35-7.31 (1H, m, Ar**H**), 7.03 (1H, d, *J* = 8.4 Hz, Ar**H**), 6.96 (1H, t, *J* = 7.6 Hz, Ar**H**), 6.44 (1H, s, =C**H**), 4.41-4.37 (2H, m, C$\mathbf{H}_2$O), 3.81-3.78 (2H, m, C$\mathbf{H}_2$N); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 168.7 (C), 162.1 (C), 155.3 (C), 136.9 (CH), 136.7 (C), 131.6 (C), 130.7 (CH), 128.8 (2 x CH), 128.4 (CH), 128.1 (2 x CH), 119.7 (CH), 117.7 (CH), 117.2 (CH), 110.9 (C), 63.1 (CH_2), 44.3 (CH_2); HRMS (ES) Exact mass calcd for $C_{18}H_{16}NO_5$ $[M+H]^+$: 326.1023, found: 326.1028.



(*E*)-1-(2-oxo-1,3-oxazolidin-3-yl)-2-phenylethenyl (2*E*,4*E*)-hexa-2,4-dienoate (143j)

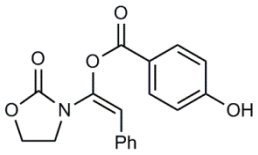
The title compound was prepared according to General Procedure D using sorbic acid (90 mg, 0.8 mmol) and purified by column chromatography (15% EtOAc/hexane→20% EtOAc/hexane) to give a colourless oil (78 mg, 65%). R_f = 0.73 (60% EtOAc/hexane); IR (film) 3061, 2991, 2913, 1767 (C=O, br), 1676, 1641, 1400, 1227, 1109, 1005 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.50-7.44 (1H, m, COCH=C**H**), 7.43-7.35 (4H, m, Ar**H**), 7.34-7.29 (1H, m, Ar**H**), 6.33 (1H, s, =C**H**Ph), 6.30-6.27 (2H, m, C**H**=C**H**Me), 5.92 (1H, d, *J* = 14.9 Hz, COC**H**=), 4.34 (2H, dd, *J* = 8.7 Hz, 7.3 Hz, C$\mathbf{H}_2$O), 3.75 (2H, dd, *J* = 8.7, 7.3 Hz, C$\mathbf{H}_2$N), 1.92 (3H, d, *J* = 4.9 Hz, C$\mathbf{H}_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 165.4 (C), 155.6 (C), 148.0 (CH), 141.6 (CH), 137.4 (C), 132.1 (C), 129.6 (CH), 128.7 (2 x CH), 128.01 (2 x CH), 127.96 (CH), 116.7 (CH), 116.0 (CH), 63.0 (CH_2), 44.4

(CH_2), 18.7 (CH_3); HRMS (ASP) Exact mass calcd for $C_{17}H_{18}NO_4$ $[M+H]^+$: 300.1230, found: 300.1230.



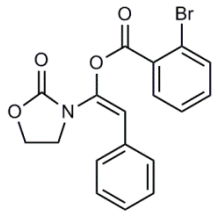
(*E*)-3-Phenylacrylic acid (*E*)-1-(2-oxo-oxazolidin-3-yl)-2-phenylvinyl ester (143k)

The title compound was prepared according to General Procedure D using *trans*-cinnamic acid (119 mg, 0.80 mmol) and purified by column chromatography (10% EtOAc/hexane→20% EtOAc/hexane) to give a colorless oil (107 mg, 80%). R_f = 0.59 (50% EtOAc/hexane); IR (film) 3059, 2987, 2917, 1766 (C=O), 1729 (C=O), 1676, 1633, 1448, 1223, 1127 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.87 (1H, d, *J* = 16.0 Hz, CH=C**H**Ph), 7.58-7.56 (2H, m, Ar**H**), 7.43-7.36 (7H, m, Ar**H**), 7.32-7.29 (1H, m, Ar**H**), 6.56 (1H, d, *J* = 16.0 Hz, C**H**=CHPh), 6.36 (1H, s, =C**H**), 4.39-4.36 (2H, m, C$\mathbf{H}_2$O), 3.78-3.75 (2H, m, C$\mathbf{H}_2$N); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 165.3 (C), 155.7 (C), 147.8 (CH), 137.5 (C), 133.9 (C), 132.1 (C), 131.0 (CH), 129.0 (2 x CH), 128.8 (2 x CH), 128.4 (2 x CH), 128.1, (3 x CH), 116.3 (CH), 116.0 (CH), 63.2 (CH_2), 44.5 (CH_2); HRMS (ES) Exact mass calcd for $C_{20}H_{18}NO_4$ $[M+H]^+$: 336.1230, found: 336.1227.



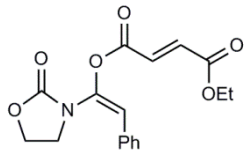
4-Hydroxybenzoic acid (*E*)-1-(2-oxo-oxazolidin-3-yl)-2-phenyl-vinyl ester (143l)

The title compound was prepared according to General Procedure D using 4-hydroxybenzoic acid (111 mg, 0.8 mmol) and purified by column chromatography (20% EtOAc/hexane→30% EtOAc/hexane) to give a white solid (63 mg, 48%). R_f = 0.48 (60% EtOAc/hexane); m.p. 162-164 °C; IR (CH_2Cl_2) 3158 (OH, br), 3054, 2986, 1757 (C=O), 1726 (C=O), 1609, 1448, 1415, 1265, 1060 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.96-7.93 (2H, m, Ar**H**), 7.56 (1H, s, O**H**), 7.43-7.36 (4H, m, Ar**H**), 7.35-7.31 (1H, m, Ar**H**), 6.90-6.86 (2H, m, Ar**H**), 6.42 (1H, s, =C**H**), 4.42 (2H, dd, *J* = 8.8 Hz, 7.4 Hz, C$\mathbf{H}_2$O), 3.70 (2H, dd, *J* = 8.8 Hz, 7.4 Hz, C$\mathbf{H}_2$N); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 164.9 (C), 162.1 (C), 156.9 (C), 137.4 (C), 132.8 (2 x CH), 132.0 (C), 128.9 (2 x CH), 128.3 (CH), 128.1 (2 x CH), 119.5 (C), 116.7 (CH), 115.7 (2 x CH), 63.7 (CH_2), 44.8 (CH_2); HRMS (ES) Exact mass calcd for $C_{18}H_{16}NO_5$ $[M+H]^+$: 326.1023, found: 326.1027.



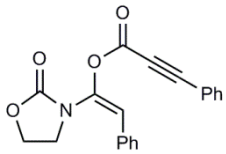
2-Bromobenzoic acid (*E*)-2 -phenyl-1-(2-oxo-oxazolidin-3-yl)-vinyl ester (143m)

The title compound was prepared according to General Procedure D using 2-bromobenzoic acid (161 mg, 0.8 mmol), heating for 19 hours. The residue was purified by column chromatography (15% EtOAc/hexane→20% EtOAc/hexane) to give a colourless gum (53 mg, 34%). R_f = 0.55 (50% EtOAc/hexane); IR (CH_2Cl_2) 3058, 2985, 2918, 1766 (C=O), 1676, 1588, 1399, 1224, 1104, 1078 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.12-8.09 (1H, m, Ar**H**), 7.73-7.70 (1H, m, Ar**H**), 7.45-7.35 (6H, m, Ar**H**), 7.34-7.30 (1H, m, Ar**H**), 6.42 (1H, s, =C**H**), 4.38 (2H, dd, *J* = 8.7 Hz, 7.3 Hz, C**H**$_2$O), 3.81 (2H, dd, *J* = 8.7 Hz, 7.3 Hz, C**H**$_2$N); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 164.1 (C), 155.6 (C), 137.5 (C), 134.6 (CH), 133.7 (CH), 132.7 (CH), 131.8 (C), 129.6 (C), 128.8 (2 x CH), 128.2 (CH), 128.1 (2 x CH), 127.5 (CH), 122.5 (C), 116.2 (CH), 63.2 (CH_2), 44.5 (CH_2); HRMS (ASP) Exact mass calcd for $C_{18}H_{15}BrNO_4$ $[M+H]^+$: 388.0179, found: 388.0178.



1-Ethyl 4-(*E*)-1-(2-oxo-1,3-oxazolidin-3-yl)-2-phenylethenyl (2E)-but-2-enedioate (143n)

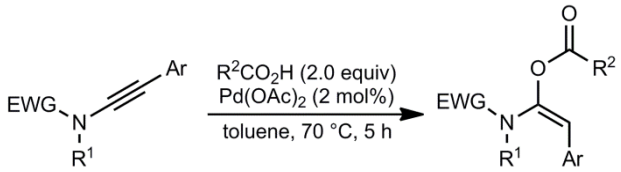
The title compound was prepared according to General Procedure D using mono-ethylfurmate (115 mg, 0.8 mmol) and purified by column chromatography (15% EtOAc/hexane→20% EtOAc/hexane) to give a 9:1 mixture of product **143n** and imide **144** as a colourless oil (83 mg, 63%). Data for **143n**: R_f = 0.68 (60% EtOAc/hexane); IR (film) 3026, 2992, 2941, 1778 (C=O), 1713 (C=O), 1645, 1389, 1261, 1219, 1039 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.29 (5H, m, Ar**H**), 7.03 (1H, d, *J* = 15.8 Hz, C**H**=CH), 6.95 (1H, d, *J* = 15.8 Hz, CH=C**H**), 6.34 (1H, s, =C**H**), 4.37 (2H, dd, *J* = 8.7 Hz, 7.3 Hz, C**H**$_2$O), 4.29 (2H, q, *J* = 7.1 Hz, C**H**$_2$CH$_3$), 3.72 (2H, dd, *J* = 8.7, 7.3 Hz, C**H**$_2$N), 1.34 (3H, t, *J* = 7.1 Hz, C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 164.3 (C), 163.2 (C), 155.3 (C), 137.0 (C), 136.1 (CH), 131.5 (C), 131.4 (CH), 128.8 (2 x CH), 128.3 (CH), 128.1 (2 x CH), 116.4 (CH), 63.1 (CH_2), 61.5 (CH_2), 44.3 (CH_2), 14.0 (CH_3); HRMS (EI) Exact mass calcd for $C_{17}H_{17}NO_6$ $[M]^+$: 331.10504, found: 331.10527.



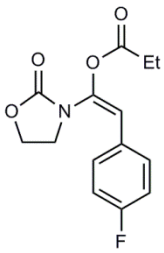
Phenylpropynoic acid (*E*)-1-(2-oxo-oxazolidin-3-yl)-2-phenylvinyl ester (143o)

The title compound was prepared according to a modification of General Procedure D in that 4.0 equivalents of phenylpropiolic acid (234 μL, 1.60 mmol) was used and the reaction time was 24 h. The residue was purified by column chromatography (10% EtOAc/hexane→20% EtOAc/hexane) to give a brown oil (98 mg, 73%). R_f = 0.54 (50% EtOAc/hexane); IR (film) 3058, 2988, 2916, 2225, 1771 (C=O), 1727 (C=O), 1678, 1400, 1280, 1139 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.64 (2H, d, *J* = 7.4 Hz, Ar**H**), 7.50 (1H, t, *J* = 7.4 Hz, Ar**H**), 7.45-7.30 (7H, m, Ar**H**), 6.42 (1H, s, =C**H**), 4.40 (2H, t, *J* = 8.0 Hz, C$\mathbf{H}_2$O), 3.76 (2H, t, *J* = 8.0 Hz, C$\mathbf{H}_2$N); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 155.3 (C), 152.0 (C), 136.6 (C), 133.3 (2 x CH), 131.6 (C), 131.2 (CH), 128.8 (2 x CH), 128.7 (2 x CH), 128.4 (CH), 128.1 (2 x CH), 118.9 (C), 117.4 (CH), 89.8 (C), 79.5 (C), 63.1 (CH_2), 44.3 (CH_2); HRMS (ES) Exact mass calcd for $C_{20}H_{16}NO_4$ $[M+H]^+$: 334.1074, found: 334.1078.

Hydroacyloxylation of Ynamides: General Procedure E

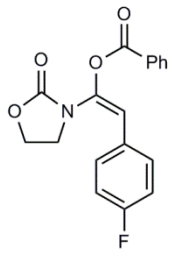


A solution of the appropriate ynamide (0.40 mmol), the appropriate carboxylic acid (0.80 mmol), and $Pd(OAc)_2$ (1.8 mg, 0.008 mmol) in toluene (4 mL) was heated at 70 °C in a sealed tube for 5 h. After cooling to room temperature, saturated aqueous $NaHCO_3$ solution (15 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography gave the desired α-acyloxyenamide.



Propionic acid (*E*)-2-(4-fluorophenyl)-1-(2-oxo-oxazolidin-3-yl)vinyl ester (146a)

The title compound was prepared according to General Procedure E using ynamide **83i** (82 mg, 0.40 mmol) and propanoic acid (60 µL, 0.80 mmol) and purified by column chromatography (20% EtOAc/hexane→30% EtOAc/hexane) to give a light green oil (86 mg, 77%). R_f = 0.51 (50% EtOAc/hexane); IR (film) 3071, 2986, 2919, 1764 (C=O), 1677, 1508, 1398, 1228, 1108, 731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30-7.27 (2H, m, Ar**H**), 7.06-7.02 (2H, m, Ar**H**), 6.19 (1H, s, =C**H**), 4.36-4.33 (2H, m, C**H**$_2$O), 3.69-3.66 (2H, m, C**H**$_2$N), 2.53 (2H, q, *J* = 7.5 Hz, C**H**$_2$CH$_3$), 1.21 (3H, t, *J* = 7.5 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 172.9 (C), 162.1 (C, d, *J* = 248.6 Hz), 155.4 (C), 137.4 (C, d, *J* = 1.6 Hz), 129.8 (2 x CH, d, *J* = 8.1 Hz), 128.1 (C, d, *J* = 3.5 Hz), 115.8 (2 x CH, d, *J* = 21.7 Hz), 114.6 (CH), 63.1 (CH$_2$), 44.4 (CH$_2$), 27.0 (CH$_2$), 8.7 (CH$_3$); ^{19}F NMR (376.3 MHz, $CDCl_3$) δ –112.8 (1F, tt, *J* = 8.5, 5.4 Hz); HRMS (ASAP) Exact mass calcd for $C_{14}H_{15}FNO_4$ $[M+H]^+$: 280.0980, found: 280.0979.

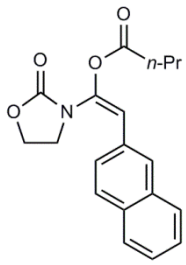


Benzoic acid (*E*)-2-(4-fluorophenyl)-1-(2-oxo-oxazolidin-3-yl)vinyl ester (146b)

Using 2.0 equiv of carboxylic acid: The title compound was prepared according to General Procedure E using ynamide **83i** (82 mg, 0.40 mmol) and benzoic acid (98 mg, 0.80 mmol) and purified by column chromatography (50% EtOAc/hexane) to give a yellow oil (106 mg, 81%). R_f = 0.60 (50% EtOAc/hexane); IR (film) 3069, 3012, 2918, 1766 (C=O), 1738 (C=O), 1678, 1508, 1398, 1227, 1085 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.14 (2H, dd, *J* = 8.3, 1.2 Hz, Ar**H**), 7.66-7.63 (1H, m, Ar**H**), 7.50 (2H, t, *J* = 7.8 Hz, Ar**H**), 7.37-7.34 (2H, m, Ar**H**), 7.09-7.06 (2H, m, Ar**H**), 6.37 (1H, s, =C**H**), 4.40-4.37 (2H, m, C**H**$_2$O), 3.81-3.78 (2H, m, C**H**$_2$N); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 165.1 (C), 162.2 (C, d, *J* = 248.8 Hz), 155.4 (C), 137.4 (C, d, *J* = 1.7 Hz), 134.1 (CH), 130.3 (2 x CH), 129.8 (2 x CH, d, *J* = 8.1 Hz), 128.6 (2 x CH), 128.2 (C), 128.1 (C, d, *J* = 3.5 Hz), 115.8 (2 x CH, d, *J* = 21.7 Hz), 115.7 (CH), 63.1 (CH$_2$), 44.4 (CH$_2$); ^{19}F NMR (376.3 MHz,

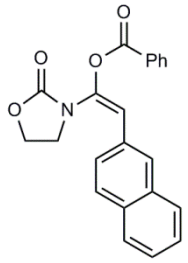
$CDCl_3$) δ –112.7 (1F, tt, *J* = 8.6, 5.4 Hz); HRMS (ASAP) Exact mass calcd for $C_{18}H_{15}FNO_4$ $[M+H]^+$: 328.0980, found: 328.0982.

Using 1.1 equiv of carboxylic acid: A repeat of the above reaction using benzoic acid (54 mg, 0.44 mmol) for a reaction time of 6 hours, under otherwise identical conditions gave the title compound (109 mg, 83%) as a yellow oil.



Propionic acid (*E*)-2-naphthalen-2-yl-1-(2-oxo-oxazolidin-3-yl)vinyl ester (146c)

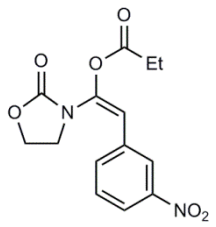
The title compound was prepared according to General Procedure E using ynamide **83h** (95 mg, 0.40 mmol) and butyric acid (73 µL, 0.80 mmol) and purified by column chromatography (15% EtOAc/hexane→20% EtOAc/hexane) to give a pale orange solid (99 mg, 76%). R_f = 0.68 (70% EtOAc/hexane); m.p. 93-95 °C; IR (neat) 2972, 2930, 2874, 1763 (C=O), 1748 (C=O), 1676, 1402, 1230, 1107, 1005 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.83-7.80 (3H, m, Ar**H**), 7.76 (1H, s, Ar**H**), 7.51-7.46 (3H, m, Ar**H**), 6.39 (1H, s, =C**H**), 4.33 (2H, t, *J* = 8.0 Hz, C$\mathbf{H}_2$O), 3.70 (2H, t, *J* = 8.0 Hz, C$\mathbf{H}_2$N), 2.53 (2H, t, *J* = 7.4 Hz, C$\mathbf{H}_2$$CH_2CH_3$), 1.77 (2H, sextet, *J* = 7.4 Hz, C$\mathbf{H}_2$$CH_3$), 1.04 (3H, t, *J* = 7.4 Hz, C$\mathbf{H}_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 172.2 (C), 155.6 (C), 137.8 (C), 133.2 (C), 132.7 (C), 129.5 (C), 128.4 (CH), 128.0 (CH), 127.7 (CH), 127.6 (CH), 126.5 (CH), 126.5 (CH), 125.3 (CH), 115.3 (CH), 63.1 (CH_2), 44.7 (CH_2), 35.5 (CH_2), 18.2 (CH_2), 13.5 (CH_3); HRMS (ES) Exact mass calcd for $C_{19}H_{20}NO_4$ $[M+H]^+$: 326.1387, found: 326.1390.



Benzoic acid (*E*)-2-naphthalen-2-yl-1-(2-oxo-oxazolidin-3-yl)vinyl ester (146d)

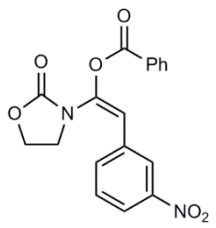
The title compound was prepared according to General Procedure E using ynamide **83h** (94.9 mg, 0.4 mmol) and benzoic acid (97.7 mg, 0.8 mmol) and purified by column chromatography (15% EtOAc/hexane) to give a cream solid (106 mg, 74%). R_f = 0.73 (60% EtOAc/hexane); m.p. 126-128 °C; IR (solid) 3068, 3028, 2895, 1761 (C=O), 1737 (C=O), 1670, 1404, 1225, 1117, 1047 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.21-8.18 (2H, m, ArH), 7.88-7.81 (4H, m, ArH), 7.68-7.64 (1H, m, Ar**H**), 7.55-7.49 (5H, m,

ArH), 6.57 (1H, s, =C**H**), 4.38 (2H, dd, *J* = 8.7, 7.4 Hz, C**H**$_2$O), 3.82 (2H, dd, *J* = 8.2, 7.8 Hz, C**H**$_2$N); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 165.2 (C), 155.6 (C), 137.9 (C), 134.0 (CH), 133.3 (C), 132.8 (C), 130.4 (2 x CH), 129.5 (C), 128.7 (2 x CH), 128.5 (CH), 128.4 (C), 128.0 (CH), 127.8 (CH), 127.6 (CH), 126.6 (CH), 126.6 (CH), 125.3 (CH), 116.4 (CH), 63.2 (CH_2), 44.7 (CH_2); HRMS (ES) Exact mass calcd for $C_{22}H_{18}NO_4$ $[M+H]^+$: 360.1230, found: 360.1235.



Propanoic acid (*E*)-2-(3-nitrophenyl)-1-(2-oxo-oxazolidin-3-yl)vinyl ester (146e)

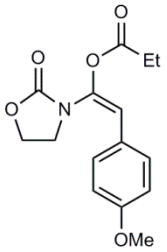
The title compound was prepared according to General Procedure E using ynamide **83j** (93 mg, 0.40 mmol) and propanoic acid (60 μL, 0.80 mmol) and purified by column chromatography (20% EtOAc/hexane→30% EtOAc/hexane) to give a cream solid (82 mg, 67%). R_f = 0.60 (70% EtOAc/hexane); m.p. 59-62 °C; IR (film) 3063, 2987, 2918, 1769 (C=O), 1674, 1530 (N-O), 1398, 1352 (N-O), 1224, 1109 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (1H, s, Ar**H**), 8.14-8.12 (1H, m, Ar**H**), 7.64 (1H, d, *J* = 7.8 Hz, Ar**H**), 7.54 (1H, t, *J* = 8.0 Hz, Ar**H**), 6.28 (1H, s, =C**H**), 4.45-4.42 (2H, m, C**H**$_2$O), 3.78-3.74 (2H, m, C**H**$_2$N), 2.57 (2H, q, *J* = 7.5 Hz, C**H**$_2$CH$_3$), 1.24 (3H, t, *J* = 7.5 Hz, C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 172.6 (C), 154.8 (C), 148.5 (C), 139.3 (C), 134.1 (C), 134.0 (CH), 129.7 (CH), 122.6 (2 x CH), 113.2 (CH), 63.0 (CH_2), 44.5 (CH_2), 27.1 (CH_2), 8.7 (CH_3); HRMS (ASAP) Exact mass calcd for $C_{14}H_{15}N_2O_6$ $[M+H]^+$: 307.0925, found: 307.0922.



Benzoic acid (*E*)-2-(3-nitrophenyl)-1-(2-oxo-oxazolidin-3-yl)vinyl ester (146f)

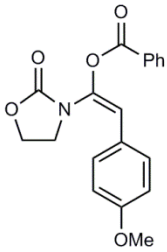
The title compound was prepared according to General Procedure E using ynamide **83j** (93 mg, 0.40 mmol) and benzoic acid (98 mg, 0.80 mmol) and purified by column chromatography (20% EtOAc/hexane→30% EtOAc/hexane) to give a cream solid (111 mg, 78%). R_f = 0.45 (50% EtOAc/hexane); m.p. 128-130 °C; IR (film) 3092, 2912, 1774 (C=O), 1745 (C=O), 1680, 1524 (N-O), 1342 (N-O), 1219, 1128, 1051 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (1H, s, Ar**H**), 8.14 (3H, d, *J* = 7.9 Hz, Ar**H**), 7.71-7.65 (2H, m, Ar**H**),

7.56 (1H, t, *J* = 8.0 Hz, Ar**H**), 7.52 (2H, t, *J* = 7.7 Hz, Ar**H**), 6.44 (1H, s, =C**H**), 4.49-4.45 (2H, m, C**H**$_2$O), 3.89-3.86 (2H, m, C**H**$_2$N); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 164.8 (C), 154.8 (C), 148.4 (C), 139.3 (C), 134.3 (CH), 134.1 (C), 134.0 (CH), 130.4 (2 x CH), 129.7 (CH), 128.7 (2 x CH), 127.9 (C), 122.63 (CH), 122.60 (CH), 114.1 (CH), 63.0 (CH_2), 44.5 (CH_2); HRMS (ASAP) Exact mass calcd for $C_{18}H_{15}N_2O_6$ $[M+H]^+$: 355.0925, found: 355.0926.



Propionic acid (*E*)-2-(4-methoxyphenyl)-1-(2-oxo-oxazolidin-3-yl)vinyl ester (146g)

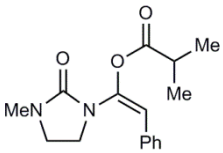
The title compound was prepared according to a slight modification of General Procedure E using ynamide **83k** (87 mg, 0.40 mmol) and propanoic acid (60 μL, 0.80 mmol) in that an increased loading of $Pd(OAc)_2$ (3.6 mg, 0.016 mmol) was employed. Purification by column chromatography (20% EtOAc/hexane→35% EtOAc/hexane) gave a white solid (50 mg, 43%). R_f = 0.53 (60% EtOAc/hexane); m.p. 106-108 °C; IR (film) 3054, 2986, 1769 (C=O), 1608, 1513, 1421, 1265, 738, 705 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (2H, d, *J* = 8.7 Hz, Ar**H**), 6.90 (2H, d, *J* = 8.7 Hz, Ar**H**), 6.19 (1H, s, =C**H**), 4.38-4.33 (2H, m, C**H**$_2$O), 3.82 (3H, s, OC**H**$_3$), 3.74-3.69 (2H, m, C**H**$_2$N), 2.54 (2H, q, *J* = 7.5 Hz, C**H**$_2$CH$_3$), 1.22 (3H, t, *J* = 7.5 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 173.2 (C), 159.3 (C), 155.7 (C), 136.2 (C), 129.4 (2 x CH), 124.3 (C), 115.4 (CH), 114.2 (2 x CH), 63.1 (CH_2), 55.2 (CH_3), 44.3 (CH_2), 27.1 (CH_2), 8.8 (CH_3); HRMS (ES) Exact mass calcd for $C_{15}H_{18}NO_5$ $[M+H]^+$: 292.1179, found: 292.1182.



Benzoic acid (*E*)-2-(4-methoxy-phenyl)-1-(2-oxo-oxazolidin-3-yl)-vinyl ester (146h)

The title compound was prepared according to General Procedure E using ynamide **83k** (86.9 mg, 0.4 mmol), benzoic acid (97.7 mg, 0.8 mmol) and $Pd(OAc)_2$ (3.6 mg, 0.016 mmol) and purified by column chromatography (20% EtOAc/hexane→30% EtOAc/hexane)to give a white solid (86.9 mg, 36%). R_f = 0.58 (60% EtOAc/hexane); m.p. 152-154 °C; IR (CH_2Cl_2) 3054, 2987, 1768 (C=O), 1736 (C=O), 1608, 1513, 1401, 1265, 1108, 1037 cm^{-1}; ^{1}H

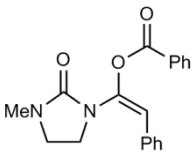
NMR (500 MHz, $CDCl_3$) δ 8.16 (2H, dd, *J* = 8.3 Hz, 1.3 Hz, Ar**H**), 7.64 (2H, app. tt, *J* = 7.5 Hz, 1.2 Hz, Ar**H**), 7.50 (2H, t, *J* = 7.8 Hz, Ar**H**), 7.33-7.30 (2H, m, Ar**H**), 6.94-6.90 (2H, m Ar**H**), 6.36 (1H, s, =C**H**), 4.39 (2H, dd, *J* = 8.7 Hz, 7.3 Hz, C**H**$_2$O), 3.84 (3H, s, OC**H**$_3$), 3.83 (2H, dd, *J* = 8.7 Hz, 7.3 Hz, C**H**$_2$N); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 165.4 (C), 159.4 (C), 155.7 (C), 136.2 (C), 134.0 (CH), 130.4 (2 x CH), 129.5 (2 x CH), 128.6 (2 x CH), 128.5 (C), 124.3 (C), 116.5 (CH), 114.2 (2 x CH), 63.2 (CH_2), 55.3 (CH_3), 44.4 (CH_2); HRMS (ES) Exact mass calcd for $C_{19}H_{18}NO_5$ $[M+H]^+$: 340.1179, found: 340.1184.



Isobutyric acid (*E*)-1-(3-methyl-2-oxoimidazolidin-1-yl)-2-phenylvinyl ester (146i)

Using 2.0 equiv of carboxylic acid: The title compound was prepared according to General Procedure E using ynamide **83m** (80 mg, 0.40 mmol) and isobutyric acid (74 μL, 0.80 mmol) and purified by column chromatography (30% EtOAc/hexane→35% EtOAc/hexane) to give a yellow oil (86 mg, 74%). R_f = 0.51 (70% EtOAc/hexane); IR (film) 3059, 2975, 2877, 1751 (C=O), 1715 (C=O), 1670, 1495, 1388, 1275, 1092 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.27 (4H, m, Ar**H**), 7.22-7.18 (1H, m, Ar**H**), 6.06 (1H, s, =C**H**), 3.51-3.36 (2H, m, C**H**$_2$N), 3.33 (2H, dd, *J* = 9.4, 6.7 Hz, C**H**$_2$N), 2.81 (3H, s, NC**H**$_3$), 2.72 (1H, septet, *J* = 7.0 Hz, C**H**$(CH_3)_2$), 1.24 (6H, d, *J* = 7.0 Hz, CH(C**H**$_3)_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 175.9 (C), 157.6 (C), 139.8 (C), 132.9 (C), 128.4 (2 x CH), 128.1 (2 x CH), 127.3 (CH), 113.3 (CH), 45.1 (CH_2), 41.7 (CH_2), 33.7 (CH), 31.0 (CH_3), 18.8 (2 x CH_3); HRMS (ASAP) Exact mass calcd for $C_{16}H_{21}N_2O_3$ $[M+H]^+$: 289.1547, found: 289.1541.

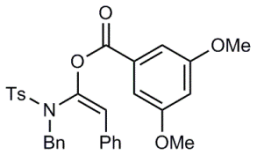
Using 1.1 equiv of carboxylic acid: A repeat of the above reaction using isobutyric acid (41 μL, 0.44 mmol) under otherwise identical conditions gave the title compound (82 mg, 71%) as a yellow oil.



Benzoic acid (*E*)-1-(3-methyl-2-oxo-imidazolidin-1-yl)-2-phenyl-vinyl ester (146j)

The title compound was prepared according to General Procedure E using ynamide **83m** (80.1 mg, 0.4 mmol) and benzoic acid (97.7 mg, 0.8 mmol) and

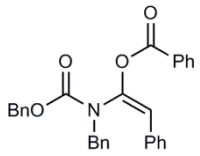
purified by column chromatography (20% EtOAc/hexane→30% EtOAc/hexane) to give a pale yellow oil (92 mg, 71%). R_f = 0.40 (60% EtOAc/hexane); IR (CH_2Cl_2) 3054, 2985, 2922 (br), 1732 (C=O), 1673, 1600, 1495, 1434, 1265, 736 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.15 (2H, app. dd, *J* = 7.2 Hz, 1.2 Hz, Ar**H**), 7.60 (1H, app. td, *J* = 7.5 Hz, 1.0 Hz, Ar**H**), 7.47 (2H, t, *J* = 7.8 Hz, Ar**H**), 7.39 (2H, app. d, *J* = 7.3 Hz, Ar**H**), 7.34 (2H, t, *J* = 7.7 Hz, Ar**H**), 7.25 (2H, t, *J* = 7.3 Hz, Ar**H**), 6.26 (1H, s, =C**H**), 3.61 (2H, dd, *J* = 9.0 Hz, 7.1 Hz, C$\mathbf{H}_2$O), 3.36 (2H, app. dd, *J* = 7.3 Hz, C$\mathbf{H}_2$N), 2.81 (3H, s, NC$\mathbf{H}_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 165.3 (C), 157.6 (C), 139.7 (C), 133.6 (CH), 132.9 (C), 130.2 (CH), 128.9(C), 128.5 (CH), 128.4 (CH), 128.1 (CH), 127.4 (CH), 114.4 (CH), 45.0 (CH_2), 41.7 (CH_2), 31.0 (NCH_3); HRMS (ES) Exact mass calcd for $C_{19}H_{19}N_2O_3$ $[M+H]^+$: 323.1390, found: 323.1394.



3,5-Dimethoxybenzoic acid (*E*)-1-[benzyl-(toluene-4-sulfonyl)amino]-2-phenylvinyl ester (151a)

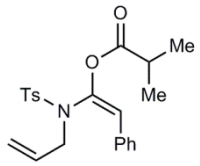
The title compound was prepared according to a slight modification of General Procedure E using ynamide **83o** (145 mg, 0.40 mmol) and 3,5-dimethoxybenzoic acid (146 mg, 0.80 mmol) in that the reaction was heated for 24 h. Purification by column chromatography (15% EtOAc/hexane) gave an orange oil (196 mg, 90%). R_f = 0.39 (30% EtOAc/hexane); IR (CH_2Cl_2) 3062, 3030, 2940, 2840, 1741 (C=O), 1665, 1596, 1456, 1353, 1205 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.77 (2H, d, *J* = 8.2 Hz, Ar**H**), 7.37-7.34 (2H, m, Ar**H**), 7.25-7.17 (7H, m, Ar**H**), 7.17-7.11 (3H, m, Ar**H**), 6.91 (2H, d, *J* = 2.3 Hz, Ar**H**), 6.68 (1H, t, *J* = 2.3 Hz, Ar**H**), 6.51 (1H, s, =C**H**), 4.50 (2H, s, C$\mathbf{H}_2$N), 3.83 (6H, s, 2 x OC$\mathbf{H}_3$) 2.36 (3H, s, ArC$\mathbf{H}_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 163.8 (C), 160.6 (2 x C), 144.0 (C), 136.9 (C), 136.5 (C), 134.4 (C), 132.0 (C), 130.8 (C), 129.6 (4 x CH), 128.7 (2 x CH), 128.2 (2 x CH), 128.11 (2 x CH), 128.06 (CH), 128.0 (CH), 127.9 (2 x CH), 123.3 (CH), 107.7 (2 x CH), 105.9 (CH), 55.6 (2 x CH_3), 52.6 (CH_2), 21.4 (CH_3); HRMS (ES) Exact mass calcd for $C_{31}H_{33}N_2O_6S$ $[M+NH_4]^+$: 561.2054, found: 561.2051.

Using 1.1 equiv of carboxylic acid: A repeat of the above reaction using 3,5-dimethoxybenzoic acid (80 mg, 0.44 mmol) under otherwise identical conditions gave the title compound (160 mg, 74%) as an orange oil.



Benzoic acid (*E*)-1-(benzylbenzyloxycarbonylamino)-2-phenylvinyl ester (151b)

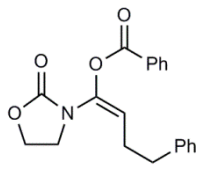
The title compound was prepared according to a slight modification of General Procedure E using ynamide **83g** (137 mg, 0.40 mmol) and benzoic acid (98 mg, 0.80 mmol) in that the reaction time was 24 h. Purification by column chromatography (10% EtOAc/hexane→20% EtOAc/hexane) gave a yellow oil (104 mg, 56%). R_f = 0.61 (30% EtOAc/hexane); IR (film) 3066, 3019, 2954, 1743 (C=O), 1712 (C=O), 1601, 1450, 1397, 1216, 1062 cm^{-1};^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (2H, br s, Ar**H**), 7.57 (1H, t, *J* = 7.5 Hz, Ar**H**), 7.40 (2H, t, *J* = 7.7 Hz, Ar**H**), 7.33 (2H, br s, Ar**H**), 7.29-7.17 (13H, m, Ar**H**), 6.38 (1H, s, =C**H**), 5.14 (2H, s, C**H**$_2$), 4.65 (2H, br s, C**H**$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 163.8 (C), 155.1 (C), 139.7 (C), 136.8 (C), 135.8 (C), 133.4 (CH), 132.7 (C), 130.0 (2 x CH), 129.1 (C), 128.7 (2 x CH), 128.6 (2 x CH), 128.3 (2 x CH), 128.3 (2 x CH), 128.3 (2 x CH), 128.0 (2 x CH), 127.9 (2 x CH), 127.8 (CH), 127.5 (CH), 117.3 (CH), 68.0 (CH_2), 51.5 (CH_2), due to overlapping signals in the aromatic region, two CH signals were not observed; HRMS (ES) Exact mass calcd for $C_{30}H_{26}NO_4$ $[M+H]^+$: 464.1856, found: 464.1849.



(*E*)-2-phenyl-1-[N-(prop-2-en-1-yl)(4-methylbenzene)sulfonamido]ethenyl 2-methylpropanoate (151c)

The title compound was prepared according to General Procedure E using ynamide **83p** (125 mg, 0.4 mmol) and isobutyric acid (74 µL, 0.8 mmol) and purified by column chromatography (10% EtOAc/hexane→20% EtOAc/hexane) to give an orange solid (90 mg, 56%). R_f = 0.77 (50% EtOAc/hexane); m.p. 65-68 °C; IR (CH_2Cl_2) 3059, 2976, 2931, 2876, 1760 (C=O), 1667, 1597, 1448, 1357, 1166 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (2H, d, *J* = 8.3 Hz, Ar**H**), 7.55 (2H, d, *J* = 7.6 Hz, Ar**H**), 7.35-7.25 (5H, m, Ar**H**), 6.37 (1H, s, =C**H**), 5.74 (1H, tdd, *J* = 16.9 Hz, 10.1 Hz, 6.8 Hz, =C**H**), 5.09 (2H, ddd, *J* = 13.6 Hz, 11.2 Hz, 1.1 Hz, =C**H**$_2$), 3.94 (2H, d, J = 6.8 Hz, C**H**$_2$N), 2.45-2.40 (1H, m, C**H**), 2.43 (3H, s, ArC**H**$_3$), 1.07 (6H, d, J = 7.0 Hz, (C**H**$_3$)$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 174.2 (C), 143.9 (C), 137.2 (C), 136.5 (C), 132.2 (C), 131.8 (CH), 129.4 (2 x CH), 128.8 (2 x CH), 128.3 (2 x CH), 128.2 (CH), 128.1 (2 x CH), 122.2 (CH),

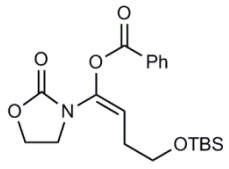
119.6 (CH_2), 52.0 (CH_2), 34.0 (CH), 21.5 (CH_3), 18.5 (2 x CH_3); HRMS (ES) Exact mass calcd for $C_{22}H_{29}N_2O_4S$ $[M+NH_4]^+$: 417.1843, found: 417.1845.



Benzoic acid (*E*)-2-(3-phenylpropyl)-1-(2-oxo-oxazolidin-3-yl)-vinyl ester (153a)

The title compound was prepared according to General Procedure E using ynamide **83c** (86.1 mg, 0.4 mmol) and benzoic acid (97.7 mg, 0.8 mmol) and purified by column chromatography (15% EtOAc/hexane→20% EtOAc/hexane) to give a colourless oil (53 mg, 39%). R_f = 0.53 (50% EtOAc/hexane); IR (CH_2Cl_2) 3060, 2922, 2857, 1770 (C=O), 1739 (C=O), 1697, 1404, 1266, 1230, 737 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.11-8.08 (2H, m, Ar**H**), 7.63 (1H, app. t, *J* = 7.5 Hz, Ar**H**), 7.48 (2H, t, *J* = 7.8 Hz, Ar**H**), 7.32 (1H, t, *J* = 7.5 Hz, Ar**H**), 7.27-7.17 (3H, m, Ar**H**), 5.49 (1H, t, *J* = 7.7 Hz, =C**H**), 4.35-4.30 (2H, app. dd, C**H**$_2$O), 3.63-3.59 (2H, app. dd, C**H**$_2$N), 2.82 (2H, t, *J* = 7.5 Hz, C**H**$_2$Ph), 2.49 (2H, q, *J* = 7.5 Hz, C**H**$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 165.0 (C), 155.5 (C), 141.1 (C), 136.5 (C), 133.9 (CH), 130.2 (CH), 128.6 (CH), 128.6 (CH), 128.4 (CH), 128.4 (C), 126.1 (CH), 117.5 (CH), 62.6 (CH_2), 44.9 (CH_2), 34.9 (CH_2), 28.3 (CH_2); HRMS (ASP) Exact mass calcd for $C_{20}H_{23}N_2O_4$ $[M+NH_4]^+$: 355.1652, found: 355.1652.

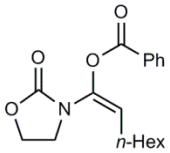
At room temperature: A repeat of the above reaction, conducting at room temperature for 24 hours using $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), under otherwise identical conditions gave the title compound (71 mg, 53%) as a colourless oil.



(1*E*)-4-[(tert-butyldimethylsilyl)oxy]-1-(2-oxo-1,3-oxazolidin-3-yl)but-1-en-1-yl benzoate (153b)

The title compound was prepared according to General Procedure E using ynamide **83b** (107.8 mg, 0.4 mmol) and benzoic acid (97.7 mg, 0.8 mmol) and purified by column chromatography (15% EtOAc/hexane→20% EtOAc/hexane) to give a colourless oil (52 mg, 33%). R_f = 0.75 (60% EtOAc/hexane); IR (CH_2Cl_2) 2956, 2929, 2857, 1772 (C=O), 1741 (C=O), 1406, 1258, 1227, 1098, 909 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.10 (2H, dd, *J* = 8.3, 1.2 Hz, Ar**H**), 7.66-7.60 (1H, m, Ar**H**), 7.51-7.46 (2H, t, *J* = 7.5 Hz,

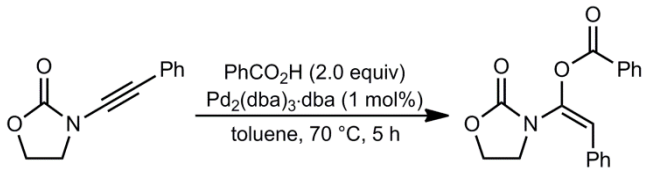
Ar**H**), 5.52 (1H, t, *J* = 7.6 Hz, =C**H**), 4.41 (2H, dd, *J* = 8.7, 7.3 Hz, C**H**$_2$O), 3.89 (2H, dd, *J* = 8.7, 7.3 Hz, C**H**$_2$N), 3.75 (2H, t, *J* = 6.5 Hz, C**H**$_2$), 2.38 (2H, app. q, C**H**$_2$), 0.90 (9H, s, C(CH$_3$)$_3$), 0.07 (6H, s, Si(CH$_3$)$_2$); ^{13}C NMR (125.8 MHz, CDCl$_3$) δ 165.0 (C), 155.6 (C), 137.1 (C), 133.9 (CH), 130.2 (2 x CH), 128.6 (2 x CH), 128.5 (C), 115.4 (CH), 62.7 (CH$_2$), 61.8 (CH$_2$), 45.3 (CH$_2$), 30.1 (CH$_2$), 25.9 (3 x CH$_3$), 18.3 (C), -5.4 (2 x CH$_3$); HRMS (ES) Exact mass calcd for $C_{20}H_{33}N_2O_5Si$ [M+NH$_4$]$^+$: 409.2153, found: 409.2148.



(1*E*)-1-(2-oxo-1,3-oxazolidin-3-yl)oct-1-en-1-yl benzoate (153c)

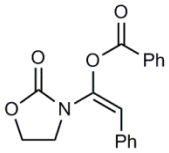
The title compound was prepared according to a modification of General Procedure E, conducting the reaction at room temperature for 24 hours, using ynamide **83d** (78.1 mg, 0.4 mmol), benzoic acid (97.7 mg, 0.8 mmol) and Pd(OAc)$_2$ (4.5 mg, 0.02 mmol). The residue was purified by column chromatography (15% EtOAc/hexane→20% EtOAc/hexane) to give a colourless oil (41 mg, 32%). R$_f$ = 0.67 (50% EtOAc/hexane); IR (CH$_2$Cl$_2$) 3059, 2928, 2858, 1770 (C=O), 1738 (C=O), 1695, 1404, 1265, 1227, 1111 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.10 (2H, dd, *J* = 8.3, 1.1 Hz, Ar**H**), 7.65-7.60 (1H, m, Ar**H**), 7.48 (2H, t, *J* = 7.8 Hz, Ar**H**), 5.46 (1H, t, *J* = 7.6 Hz, =C**H**), 4.42 (2H, dd, *J* = 8.7, 7.3 Hz, C**H**$_2$O), 3.88 (2H, dd, *J* = 8.6, 7.3 Hz, C**H**$_2$N), 2.15 (2H, q, *J* = 7.5 Hz, C**H**$_2$), 1.52-1.44 (2H, m, C**H**$_2$), 1.41-1.25 (6H, m, (C**H**$_2$)$_3$), 0.90 (3H, t, J = 6.9 Hz, C**H**$_3$); ^{13}C NMR (125.8 MHz, CDCl$_3$) δ 165.3 (C), 155.6 (C), 136.0 (C), 133.9 (CH), 130.2 (2 x CH), 128.6 (2 x CH), 128.5 (C), 119.1 (CH), 62.7 (CH$_2$), 45.4 (CH$_2$), 31.6 (CH$_2$), 28.9 (CH$_2$), 28.7 (CH$_2$), 26.3 (CH$_2$), 22.5 (CH$_2$), 14.1 (CH$_3$); HRMS (ES) Exact mass calcd for $C_{18}H_{24}NO_4$ [M+H]$^+$: 318.1700, found: 318.1706.

Hydroacyloxylation using of Pd$_2$(dba)$_3$·dba: General Procedure F



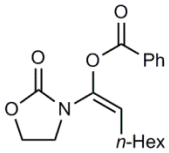
A solution of ynamide (0.20 mmol), benzoic acid (49 mg, 0.40 mmol), and Pd$_2$(dba)$_3$·dba (2.3 mg, 0.002 mmol) in toluene (2 mL) was heated at 70 °C in a sealed tube for 5 h. After cooling to room temperature, saturated aqueous NaHCO$_3$

solution (15 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography gave the desired α-acyloxyenamide.



Benzoic acid (*E*)-1-(2-oxo-oxazolidin-3-yl)-2-phenylvinyl ester (143f)

The title compound was prepared according to General Procedure F, using ynamide **83a** (37 mg, 0.20 mmol) and then purified by column chromatography (20% EtOAc/hexane) to give a colourless gum (56 mg, 90%).

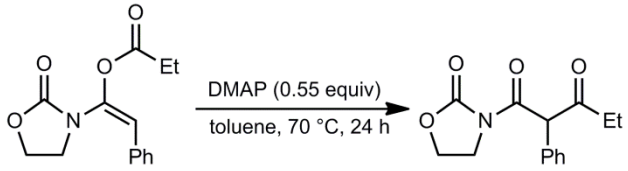


(1*E*)-1-(2-oxo-1,3-oxazolidin-3-yl)oct-1-en-1-yl benzoate (153c)

The title compound was prepared according to General Procedure F, using ynamide **83d** (39 mg, 0.2 mmol) and then purified by column chromatography (15% EtOAc/hexane→20% EtOAc/hexane) to give a colourless oil (12 mg, 19%).

Further Reactions of α-Acyloxyenamide 143b

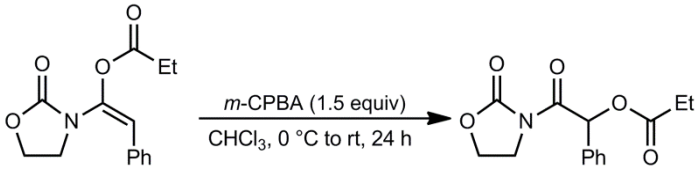
1-(2-Oxo-oxazolidin-3-yl)-2-phenylpentane-1,3-dione (161)



A solution of α-acyloxyenamide **143b** (105 mg, 0.40 mmol) and DMAP (27 mg, 0.22 mmol) in toluene (8 mL) was heated at 70 ºC for 16 h. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography (15% EtOAc/hexane→23% EtOAc/hexane) to give the β-ketoimide **161** (95 mg, 91%) as a white solid. R_f = 0.55 (60% EtOAc/hexane); m.p. 116-118 °C; IR (solid) 2964, 2924, 1757 (C=O), 1703 (C=O), 1487, 1394, 1238, 1109, 1039, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41-7.32 (3H, m, Ar**H**), 7.29-7.26 (2H, m, Ar**H**), 5.83 (1H, s, C**H**Ph), 4.50-4.39 (2H, m, C$\mathbf{H}_2$O), 4.14 (1H, ddd, *J* = 10.9, 9.5, 7.0 Hz, C$\mathbf{H}_2$N), 4.02 (1H, ddd, *J* = 10.9, 9.3, 6.8 Hz, C$\mathbf{H}_2$N), 2.67 (1H, dq, *J* = 18.2, 7.3 Hz, C$\mathbf{H}_2$$CH_3$), 2.40 (1H, dq, *J* = 18.2, 7.3 Hz, C$\mathbf{H}_2$$CH_3$), 0.99 (3H, t, *J* = 7.3 Hz, CH_2C$\mathbf{H}_3$); ^{13}C

NMR (125.8 MHz, $CDCl_3$) δ 205.1 (C), 168.0 (C), 153.9 (C), 131.8 (C), 130.2 (2 x CH), 128.8 (2 x CH), 128.4 (CH), 64.3 (CH), 62.4 (CH_2), 42.6 (CH_2), 34.6 (CH_2), 7.6 (CH_3); HRMS (ES) Exact mass calcd for $C_{14}H_{16}NO_4$ $[M+H]^+$: 262.1074, found: 262.1070.

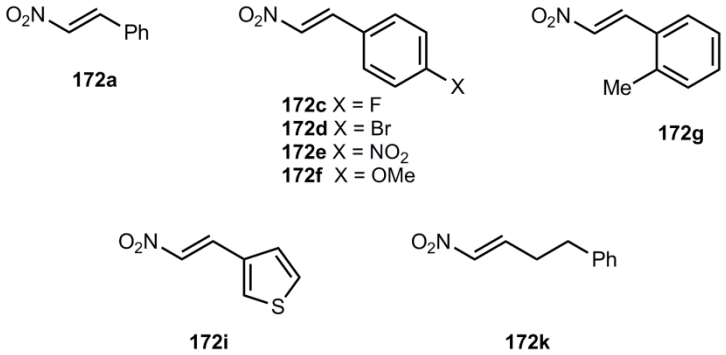
Propionic acid 2-oxo-2-(2-oxo-oxazolidin-3-yl)-1-phenylethyl ester (164)



To a solution of *m*-CPBA (223 mg, 70%, 0.90 mmol) in $CHCl_3$ (3 mL) at 0 ºC was rapidly added a solution of α-acyloxyenamide **143b** (78 mg, 0.30 mmol) in $CHCl_3$ (2 mL + 1 mL rinse) *via* cannula. The reaction was allowed to warm to room temperature over 2 h, and then stirred for a further 22 h. Saturated aqueous Na_2SO_3 solution (10 mL) was added and the mixture was stirred for 30 min. The mixture was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (2 x 20 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (40% Et_2O/hexane→45% Et_2O/hexane) gave the *α-acyloxyimide* **164** (66 mg, 79%) as a colorless oil. R_f = 0.34 (80% Et_2O/hexane); IR (film) 3023, 2986, 2926, 1784 (C=O), 1739 (C=O), 1712 (C=O), 1389, 1217, 1176, 757 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.61-7.56 (2H, m, Ar**H**), 7.41-7.37 (3H, m, Ar**H**), 7.06 (1H, s, C**H**Ph), 4.47-4.42 (1H, m, C$\mathbf{H}_2$O), 4.37-4.32 (1H, m, C$\mathbf{H}_2$O), 4.11 (1H, ddd, *J* = 10.8, 9.6, 7.2 Hz, C$\mathbf{H}_2$N), 3.90 (1H, ddd, *J* = 10.9, 9.4, 6.3 Hz, C$\mathbf{H}_2$N), 2.50 (1H, dq, *J* = 16.7, 7.6 Hz, C$\mathbf{H}_2$$CH_3$), 2.43 (1H, dq, *J* = 16.7, 7.5 Hz, C$\mathbf{H}_2$$CH_3$), 1.18 (3H, t, *J* = 7.5 Hz, CH_2C$\mathbf{H}_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 174.2 (C), 169.0 (C), 152.8 (C), 132.8 (C), 129.5 (CH), 129.0 (2 x CH), 128.7 (2 x CH), 73.3 (CH), 62.5 (CH_2), 42.4 (CH_2), 27.1 (CH_2), 8.8 (CH_3); HRMS (ES) Exact mass calcd for $C_{14}H_{19}N_2O_5$ $[M+NH_4]^+$: 295.1288, found: 295.1294.

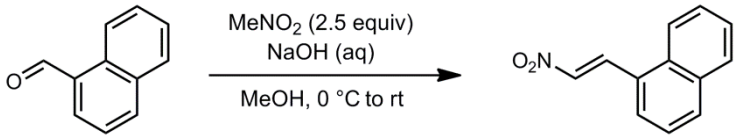
5.4 Chapter 4 Experimental

Preparation of Nitroalkenes



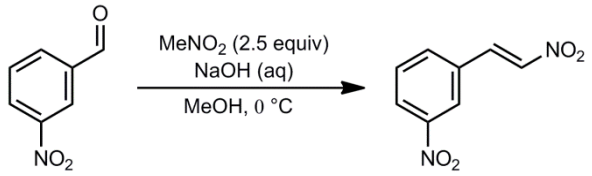
Nitroalkenes **172a** and **172f** are commercially available. Nitroalkenes **172c**,[120] **172d**,[120] **172e**,[121] **172g**,[122] **172i**,[123] and **172k**[124] were prepared by other members of the Lam group following reported procedures.

1-[(*E*)-2-Nitroethenyl]naphthalene (172b)



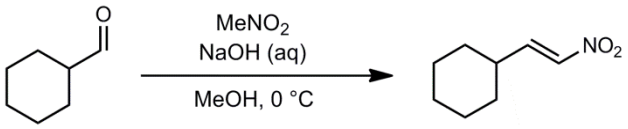
To a solution of 1-naphthaldehyde (6.25 g, 40 mmol) and nitromethane (5.45 mL, 100 mmol) in MeOH (40 mL) at 0°C was added 50% aqueous NaOH (8 mL, 2.5 equiv). The reaction mixture was stirred for 16 hours, allowing to slowly warm to room temperature. Then crushed ice was added to the mixture until the solid present dissolved and the resulting mixture was dropped into vigorously stirred 6M HCl (aq, 250 mL). The solid produced was recovered by filtration, washing with water, and then recrystallized from methanol to give nitroalkene **172b** (2.11 g, 26%) as a yellow crystalline solid. The mother liquors were diluted with CH_2Cl_2 (100 mL), dried ($MgSO_4$), filtered and evaporated, to give a yellow solid, which was recrystallized from methanol to give further nitroalkene **172b** (2.36 g, 30%) as a yellow crystalline solid. Spectral data was in agreement with literature data.[125]

1-Nitro-3-[(*E*)-2-nitroethenyl]benzene (172h)



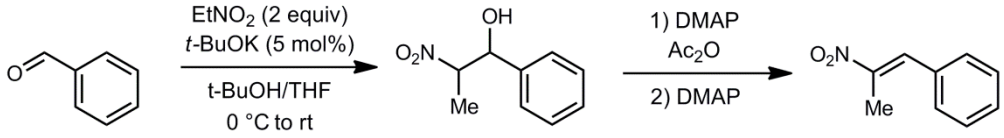
The title compound was prepared by ERAMUS student Sophie Moreau. To a solution of 3-nitrobenzaldehyde (2.0 g, 13 mmol) and nitromethane (1.98 g, 32.5 mmol) in MeOH, at 0°C, was added aqueous NaOH (10.5 M, 2.5 equiv). The reaction mixture was stirred for 40 min and then crushed ice was added until all solid precipate was dissolved. The resulting solution was slowly added to a vigorously stirred solution of 5M HCl (aq). The solid produced was recovered by filtration, washing with water, and then recrystallised from acetone, to give nitroalkene **172h** as a pale yellow crystalline solid (0.92 g, 41 %). The spectral data was in agreement with literature data.[126]

[(*E*)-2-Nitroethenyl]cyclohexane (172j)



Following a literature literature procedure:[127] To a solution of cyclohexanecarboxyaldehyde (2.00 g, 17.8 mmol) and nitromethane (1.09 g, 17.8 mmol) in methanol (4 mL) at 0 °C, was added dropwise a solution of NaOH (0.78 g, 19.6 mmol) in water (2 mL). The reaction mixture was then stirred at 0 °C until a white solid formed. Methanol (3 mL) and ice-water (16 mL) were added and the resulting slurry was stirred for 10 min at 0 °C. The mixture was then acidified using HCl (1.0 M, aq) and the resulting solution extracted with Et_2O (20 mL x 3). The combined organic phases were washed with brine, dried ($MgSO_4$) and the solvent evaporated. The residue was purified by column chromatography (5→10% EtOAc/hexane) to give nitroalkene **172j** as a yellow oil (0.55 g, 20 %). The spectral data was in agreement with literature data.[127]

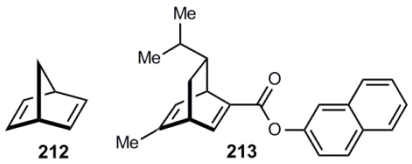
(*E*)-2-Nitro-1-phenylprop-1-ene (172l)



Following a literature procedure:[128] To a solution of benzaldehyde (4.18 g, 39 mmol) and nitroethane (5.66 mL, 79 mmol) in a mixture of *t*-BuOH (10 mL) and THF (10 mL) at 0°C was added powdered *t*-BuOK (0.22 g, 5 mol%). The reaction mixture was stirred for 16 hours, allowing to warm to room temperature. Then the mixture was diluted with Et_2O (100 mL) and washed with saturated $NaHCO_3$ (100 mL), then H_2O (50 mL). The combined aqueous layers were extracted using Et_2O (100 mL), then all organic layers were combined, washed with brine (50 mL), dried ($MgSO_4$), filtered and evaporated. This gave the alcohol intermediate (7.25 g) as mixture of diastereomers (62:38 *syn* to *anti*), which was taken on to the next step without purification.

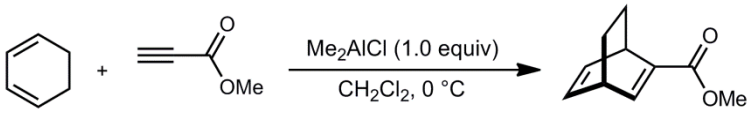
To a solution of 2-nitro-1-phenylpropan-1-ol (7.25 g, 39 mmol) in Et_2O (50 mL) was added DMAP (73 mg, 1.5 mol%). then acetic anhydride (4.2 mL, 1.1 equiv). The reaction mixture was stirred for 40 minutes at room temperature, then further DMAP (30 mg, 0.6 mol%) was added and the mixture stirred for a further 1.5 hours. The mixture was concentrated under reduced pressure. The residue was then diluted with CH_2Cl_2 (50 mL) and then DMAP (5.86 g, 1.2 equiv) was added. The mixture was stirred for 16 hours at room temperature. The mixture was then diluted with CH_2Cl_2 (50 mL) and washed with H_2O (50 mL), then 0.2M HCl (aq, 50 mL). The combined aqueous layers were extracted using CH_2Cl_2 (2 x 50 mL), then all organic layers were combined, washed with brine (50 mL), dried ($MgSO_4$), filtered and evaporated. This gave a bright green solid, which was recrystallised from MeOH, to give nitroalkene **172l** (5.07 g, 78%). Spectral data was in agreement with literature data.[129]

Preparation of Diene Ligands



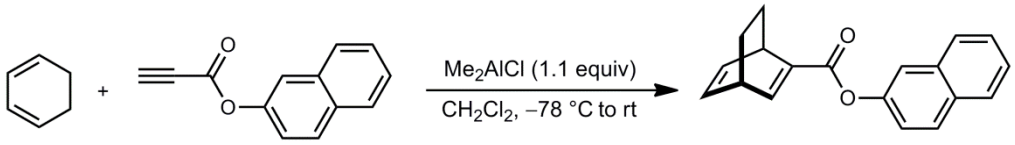
Bicyclo[2.2.1]hepta-2,5-diene (**212**) was purchased from Sigma Aldrich. Ligand **213** was prepared according to a literature procedure,[108] by other members of the Lam group.

Bicyclo[2.2.2]octa-2,5-diene-2-carboxylic acid methyl ester (*rac*-214)



To a solution of 1,3-cyclohexadiene (0.20 mL, 2.10 mmol) and methylpropiolate (0.18 mL, 2.00 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added Me_2AlCl (1.0 M in hexane, 2.0 mL, 2.00 mmol). The resulting mixture was stirred at 0 °C for 6 h, and then H_2O (10 mL) was slowly added. The mixture was extracted with Et_2O (3 x 15 mL) and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/hexane) gave *rac*-**214** (143 mg, 44%) as a colourless oil. Spectral data was in agreement with literature data.[130]

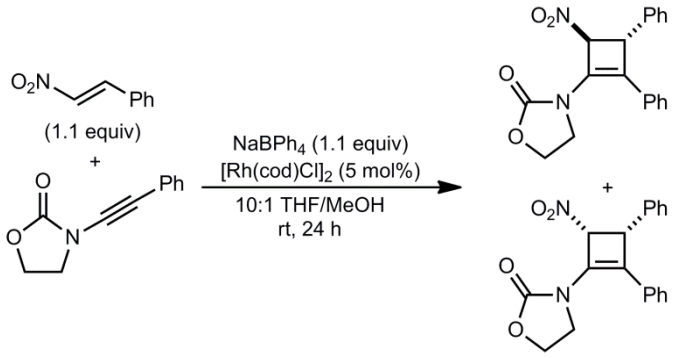
Bicyclo[2.2.2]octa-2,5-diene-2-carboxylic acid naphthalen-2-yl ester (*rac*-215)



Following a slight modification of a literature procedure:[108] To a solution of 1,3-cyclohexadiene (1.57 mL, 16.5 mmol) and 2-naphthyl propiolate[108] (2.94 g, 15.0 mmol) in CH_2Cl_2 (50 mL) at –78 °C was added Me_2AlCl (1.0 M in hexane, 16.5 mL, 16.5 mmol) over 10 min. The resulting mixture was stirred for 21 h, allowing to warm slowly to room temperature. The solution was carefully poured into vigorously stirred, ice-cooled 1 M HCl (aqueous, 150 mL). The mixture was filtered through a pad of celite using CH_2Cl_2 (50 mL) as eluent. The filtrate was then extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with brine (150

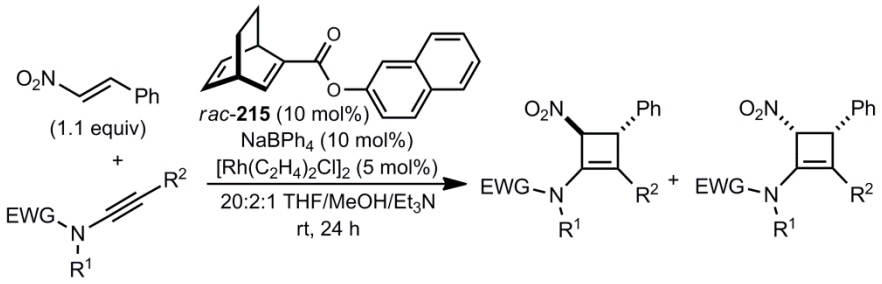
mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5→10% EtOAc/hexane) gave a solid (3.30 g) that was triturated using 20:1 hexane/EtOAc (50 mL) to leave the product *rac*-**215** (2.17 g, 53%) as a white solid. R_f = 0.49 (10% EtOAc/hexane); m.p. 131-133 ºC; IR (solid) 3053, 2953, 2870, 1714 (C=O), 1625, 1506, 1354, 1238, 1209, 1146 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.90-7.85 (2H, m, Ar**H**), 7.84-7.80 (1H, m, Ar**H**), 7.65-7.61 (2H, m, Ar**H**), 7.49 (2H, quin d, *J* = 6.9, 1.4 Hz, Ar**H**), 7.30 (1H, dd, *J* = 8.9, 2.3 Hz, =C**H**), 6.52-6.48 (1H, m, =C**H**), 6.39-6.35 (1H, m, =C**H**), 4.40-4.37 (1H, m, CH_2C**H**), 3.89 (1H, td, *J* = 6.2, 1.4 Hz, CH_2C**H**), 1.52-1.40 (4H, m, C$\mathbf{H_2}$C$\mathbf{H_2}$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 163.4 (C), 148.6 (C), 148.2 (CH), 138.2 (C), 134.8 (CH), 133.8 (C), 132.8 (CH), 131.3 (C), 129.3 (CH), 127.7 (CH), 127.6 (CH), 126.4 (CH), 125.5 (CH), 121.4 (CH), 118.6 (CH), 38.1 (CH), 36.6 (CH), 24.6 (CH_2), 24.3 (CH_2); HRMS (ESI) Exact mass calcd for $C_{19}H_{16}O_2Na$ $[M+Na]^+$: 299.1043, found: 299.1038.

Rh-Catalyzed [2+2] Cycloaddition of Ynamide 83a with Nitroalkene 172a

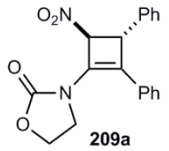


A solution of $[Rh(cod)Cl]_2$ (7.4 mg, 0.015 mmol), $NaBPh_4$ (113 mg, 0.33 mmol), ynamide **83a** (56 mg, 0.30 mmol) and nitroalkene **172a** (49 mg, 0.33 mmol) in THF (3.0 mL) and MeOH (0.3 mL) was stirred at room temperature for 24 h. Then the reaction mixture was filtered through a short plug of silica gel using EtOAc (40 mL) as eluent, and the filtrate concentrated *in vacuo*. Purification of the residue by column chromatography (15→30% EtOAc/hexane) gave the *cyclobutenamide* **209a** (43 mg, 43%) as an amorphous yellow foam followed by the *cyclobutenamide* **210a** (15 mg, 15%) as a cream solid.

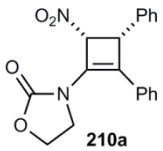
Rh-Catalyzed [2+2] Cycloaddition of Ynamides with Nitroalkene 172a: General Procedure G



A solution of $[Rh(C_2H_4)_2Cl]_2$ (5.8 mg, 0.015 mmol), *rac*-**215** (8.3 mg, 0.03 mmol), and $NaBPh_4$ (10.3 mg, 0.03 mmol) in THF (0.5 mL) was stirred at room temperature for 15 min. A solution of the appropriate ynamide (0.30 mmol) and nitroalkene **172a** (49 mg, 0.33 mmol) in THF (2.5 mL) and MeOH (0.3 mL) was then added *via* cannula. Et_3N (150 μL) was added and the mixture was stirred at room temperature for 24 h, filtered through a short plug of silica gel using EtOAc (40 mL) as eluent, and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography provided the cyclobutenamides.



209a



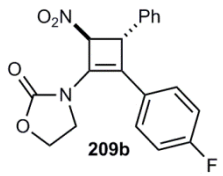
210a

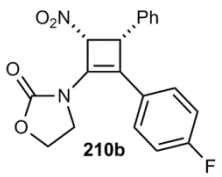
3-(4-Nitro-2,3-diphenylcyclobut-1-enyl)oxazolidin-2-one (209a/210a)

General Procedure G was followed using ynamide **83a** (56 mg, 0.30 mmol) and purification by column chromatography (20→30% EtOAc/hexane) gave the *cyclobutenamide* **209a** (60 mg, 59%) as an amorphous yellow foam followed by the *cyclobutenamide* **210a** (14 mg, 14%) as a cream solid.

Data for **209a**: R_f = 0.43 (50% EtOAc/hexane); IR (solid) 3059, 3032, 2920, 1755 (C=O), 1681, 1547, 1404, 1225, 754, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45-7.20 (10H, m, Ar**H**), 5.65 (1H, d, *J* = 1.3 Hz, C**H**NO_2), 4.58-4.50 (2H, m, C$\mathbf{H}_2$O), 4.42 (1H, d, *J* = 1.3 Hz, C**H**Ph), 4.18 (1H, dt, *J* = 8.9, 6.1 Hz, C$\mathbf{H}_2$N), 3.77 (1H, dt, *J* = 9.0, 7.8 Hz, C$\mathbf{H}_2$N); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 155.7 (C), 136.8 (C), 130.5 (C), 129.6 (C), 128.92 (CH), 128.89 (2 x CH), 128.7 (2 x CH), 128.2 (CH), 128.0 (2 x CH), 127.4 (2 x CH), 125.5 (C), 85.0 (CH), 63.3 (CH_2), 51.6 (CH), 44.7 (CH_2); HRMS (ESI) Exact mass calcd for $C_{19}H_{20}N_3O_4$ $[M+NH_4]^+$: 354.1448, found: 354.1456.

Data for **210a**: R_f = 0.37 (50% EtOAc/hexane); m.p. 118-121 ºC; IR (film) 3063, 3020, 2928, 1761 (C=O), 1678, 1551, 1406, 1217, 767, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42-7.29 (10H, m, Ar**H**), 6.18 (1H, d, *J* = 5.2 Hz, C**H**NO_2), 4.77 (1H, d, *J* = 5.2 Hz, C**H**Ph), 4.61-4.50 (2H, m, C$\mathbf{H}_2$O), 4.10 (1H, dt, *J* = 8.9, 6.0 Hz, C$\mathbf{H}_2$N), 4.02 (1H, dt, *J* = 9.1, 7.7 Hz, C$\mathbf{H}_2$N); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 155.6 (C), 134.4 (C), 131.0 (C), 128.9 (C), 128.7 (CH), 128.69 (2 x CH), 128.6 (CH), 128.52 (2 x CH), 128.50 (2 x CH), 128.0 (2 x CH), 126.1 (C), 83.7 (CH), 63.2 (CH_2), 50.5 (CH), 45.1 (CH_2); HRMS (ASAP) Exact mass calcd for $C_{19}H_{17}N_2O_4$ $[M+H]^+$: 337.1183, found: 337.1179.





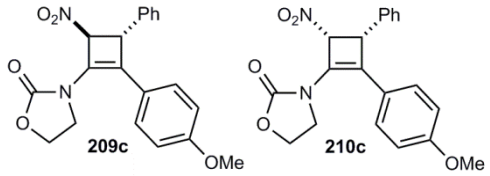
3-[2-(4-Fluorophenyl)-4-nitro-3-phenylcyclobut-1-enyl]oxazolidin-2-one (209b/210b)

General Procedure G was followed using using ynamide **83i** (62 mg, 0.30 mmol) and purification by column chromatography (15→30% EtOAc/hexane) gave **209b** as an amorphous pale yellow foam (63 mg, 59%) followed by **210b** as a pale yellow solid (15 mg, 14%).

Data for **209b**: R_f = 0.52 (50% EtOAc/hexane); IR (solid) 3061, 3028, 2926, 1749 (C=O), 1680, 1601, 1549, 1404, 1227, 752 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34-7.28 (3H, m, Ar**H**), 7.28-7.20 (4H, m, Ar**H**), 7.08-7.03 (2H, m, Ar**H**), 5.62 (1H, d, *J* = 1.2 Hz, C**H**NO_2), 4.59-4.51 (2H, m, C$\mathbf{H}_2$O), 4.38 (1H, d, *J* = 1.2 Hz, C**H**Ph), 4.13 (1H, dt, *J* = 8.7, 6.5 Hz, C$\mathbf{H}_2$N), 3.79-3.73 (1H, m, C$\mathbf{H}_2$N); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 162.8 (C, d, *J* = 250.8 Hz), 155.6 (C), 136.5 (C), 129.9 (2 x CH, d, *J* = 8.4 Hz), 129.0 (2 x CH), 128.9 (C), 128.3 (CH), 127.4 (2 x CH), 126.7 (C, d, *J* = 3.4 Hz), 125.3 (C, d, *J* = 1.5 Hz), 116.0 (2 x CH, d, *J* = 21.9 Hz), 85.0 (CH), 63.2 (CH_2), 51.6 (CH), 44.6 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –110.6 (1F, tt, *J* = 8.5, 5.3 Hz, Ar**F**); HRMS (ESI) Exact mass calcd for $C_{19}H_{15}N_2O_4FNa$ $[M+Na]^+$: 377.0908, found: 377.0908.

Data for **210b**: R_f = 0.43 (50% EtOAc/hexane); m.p. 45-48 ºC; IR (film) 3066, 3020, 2941, 1760 (C=O), 1680, 1602, 1550, 1406, 1215, 752 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33-7.29 (3H, m, Ar**H**), 7.29-7.22 (4H, m, Ar**H**), 7.06-7.01 (2H, m, Ar**H**), 6.14 (1H, d, *J* = 5.2 Hz, C**H**NO_2), 4.74 (1H, d, *J* = 5.2 Hz, C**H**Ph), 4.59 (1H, dt, *J* =

9.0, 6.0 Hz, C**H**$_2$O), 4.55 (1H, dt, *J* = 8.8, 7.7 Hz, C**H**$_2$O), 4.07 (1H, dt, *J* = 8.9, 6.0 Hz, C**H**$_2$N), 4.00 (1H, dt, *J* = 9.0, 7.7 Hz, C**H**$_2$N); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 162.8 (C, d, *J* = 250.9 Hz), 155.5 (C), 134.1 (C), 129.9 (2 x CH, d, *J* = 8.4 Hz), 128.7 (CH), 128.6 (2 x CH), 128.5 (2 x CH), 128.4 (C), 127.2 (C, d, *J* = 3.4 Hz), 125.7 (C, d, *J* = 1.6 Hz), 115.9 (2 x CH, d, *J* = 21.9 Hz), 83.7 (CH), 63.1 (CH_2), 50.4 (CH), 45.0 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –110.5 (1F, tt, *J* = 8.5, 5.3 Hz, Ar**F**); HRMS (ASAP) Exact mass calcd for $C_{19}H_{16}N_2O_4F$ $[M+H]^+$: 355.1089, found: 355.1081.



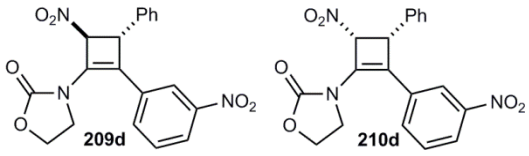
3-[2-(4-Methoxyphenyl)-4-nitro-3-phenylcyclobut-1-enyl]oxazolidin-2-one (209c/210c)

General Procedure G was followed using ynamide **83k** (65 mg, 0.30 mmol) and purification by column chromatography (20→30% EtOAc/hexane) gave **209c** as a cream foam (61 mg, 55%) followed by **210c** as a pale yellow solid (16 mg, 15%).

Data for **209c**: R_f = 0.34 (50% EtOAc/hexane); IR (solid) 3059, 3009, 2922, 1755 (C=O), 1684, 1604, 1545, 1402, 1250, 1174 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.26 (3H, m, Ar**H**), 7.26-7.22 (2H, m, Ar**H**), 7.22-7.18 (2H, m, Ar**H**), 6.89-6.86 (2H, m, Ar**H**), 5.60 (1H, d, *J* = 1.4 Hz, C**H**NO_2), 4.58-4.50 (2H, m, C**H**$_2$O), 4.37 (1H, d, *J* = 1.4 Hz, C**H**Ph), 4.16 (1H, dt, *J* = 8.7, 6.3 Hz, C**H**$_2$N), 3.80 (3H, s, OC**H**$_3$), 3.80-3.73 (1H, m, C**H**$_2$N); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 160.1 (C), 155.8 (C), 136.9 (C), 130.8 (C), 129.5 (2 x CH), 128.9 (2 x CH), 128.1 (CH), 127.5 (2 x CH), 123.5 (C), 122.9 (C), 114.3 (2 x CH), 85.3 (CH), 63.2 (CH_2), 55.3 (CH_3), 51.5 (CH), 44.7 (CH_2); HRMS (ESI) Exact mass calcd for $C_{20}H_{22}N_3O_5$ $[M+NH_4]^+$: 384.1554, found: 384.1558.

Data for **210c**: R_f = 0.29 (50% EtOAc/hexane); m.p. 54-57 ºC; IR (solid) 3041, 2959, 2924, 1753 (C=O), 1605, 1546, 1402, 1244, 1209, 1176 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.27 (5H, m, Ar**H**), 7.22-7.18 (2H, m, Ar**H**), 6.88-6.85 (2H, m, Ar**H**), 6.13 (1H, d, *J* = 5.2 Hz, C**H**NO_2), 4.72 (1H, d, *J* = 5.2 Hz, C**H**Ph), 4.61-4.51 (2H, m, C**H**$_2$O), 4.13 (1H, tt, *J* = 12.2, 4.4 Hz, C**H**$_2$N), 4.01 (1H, td, *J* = 16.9, 8.5 Hz, C**H**$_2$N), 3.80 (3H, s, OC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 160.1 (C), 155.7

(C), 134.5 (C), 130.4 (C), 129.5 (2 x CH), 128.9 (CH), 128.51 (2 x CH), 128.47 (2 x CH), 124.0 (C), 123.4 (C), 114.2 (2 x CH), 83.8 (CH), 63.2 (CH_2), 55.3 (CH_3), 50.2 (CH), 45.2 (CH_2); HRMS (ESI) Exact mass calcd for $C_{20}H_{22}N_3O_5$ $[M+NH_4]^+$: 384.1554, found: 384.1557.

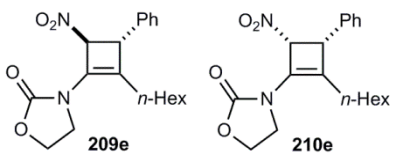


3-[4-Nitro-2-(3-nitrophenyl)-3-phenylcyclobut-1-enyl]oxazolidin-2-one (209d/210d)

General Procedure G was followed using ynamide **83j** (70 mg, 0.30 mmol) and purification by column chromatography (20→40% EtOAc/hexane) gave a mixture of **209d** and **210d** that could not be completely separated (83:17 ratio, respectively) as a pale yellow foam (55 mg, 48%). IR (solid) 3088, 3030, 2924, 1757 (C=O), 1682, 1549, 1527, 1404, 1346, 1226 cm^{-1}; HRMS (ESI) Exact mass calcd for $C_{19}H_{19}N_4O_6$ $[M+NH_4]^+$: 399.1299, found: 399.1302.

Data for **209d**: R_f = 0.24 (50% EtOAc/hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 8.16 (1H, td, *J* = 7.2, 2.1 Hz, Ar**H**), 8.15-8.13 (1H, m, Ar**H**), 7.56-7.50 (2H, m, Ar**H**), 7.35-7.30 (3H, m, Ar**H**), 7.25-7.22 (2H, m, Ar**H**), 5.67 (1H, *J* = 1.3 Hz, C**H**NO_2), 4.65-4.54 (2H, m, C**H**$_2$O), 4.46 (1H, d, *J* = 1.3 Hz, C**H**Ph), 4.18 (1H, dt, *J* = 9.0, 6.3 Hz, C**H**$_2$N), 3.79 (1H, dt, *J* = 9.0, 7.1 Hz, C**H**$_2$N); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 155.3 (C), 148.3 (C), 136.0 (C), 133.4 (CH), 132.2 (C), 129.9 (CH), 129.1 (2 x CH), 128.6 (CH), 128.0 (C), 127.3 (2 x CH), 125.5 (C), 123.3 (CH), 122.62 (CH), 84.7 (CH), 63.3 (CH_2), 51.6 (CH), 44.6 (CH_2).

Distinguishable **210d** data: R_f = 0.18 (50% EtOAc/hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 8.19-8.13 (2H, m, Ar**H**), 7.55-7.50 (2H, m, Ar**H**), 7.35-7.30 (3H, m, Ar**H**), 6.19 (1H, d, *J* = 5.2 Hz, C**H**NO_2), 4.83 (1H, d, *J* = 5.2 Hz, C**H**Ph), 4.13-4.01 (2H, m, C**H**$_2$N); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 155.1 (C), 148.3 (C), 123.2 (CH), 122.58 (CH), 83.7 (CH), 63.2 (CH), 50.1 (CH_2), 44.9 (CH_2).



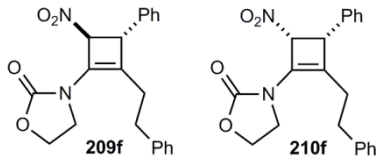
3-(2-Hexyl-4-nitro-3-phenylcyclobut-1-enyl)oxazolidin-2-one (209e/210e)

General Procedure G was followed using ynamide

83d (59 mg, 0.30 mmol) and purification by column chromatography (1% EtOAc/CH_2Cl_2) gave an 85:15 inseparable mixture of **209e** and **210e** as a brown oil (60 mg, 77%). R_f = 0.57 (50% EtOAc/hexane); IR (film) 3028, 2936, 2860, 1759 (C=O), 1705, 1551, 1412, 1244, 1105, 700 cm^{-1}; HRMS (ASAP) Exact mass calcd for $C_{19}H_{25}N_2O_4$ $[M+H]^+$: 345.1809, found: 345.1802.

Data for **209e**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.39-7.29 (3H, m, Ar**H**), 7.25-7.20 (2H, m, Ar**H**), 5.48-5.46 (1H, m, C**H**NO_2), 4.56-4.47 (2H, m, C$\mathbf{H}_2$O), 4.10-3.99 (2H, m, C$\mathbf{H}_2$N), 3.90 (1H, app s, C**H**Ph), 2.33 (1H, td, *J* = 15.2, 7.5 Hz, =CC$\mathbf{H}_2$), 2.11-2.03 (1H, m, =CC$\mathbf{H}_2$), 1.42-1.18 (8H, m, (C$\mathbf{H}_2$)$_4$), 0.86 (3H, t, *J* = 7.0 Hz, C$\mathbf{H}_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 155.1 (C), 137.1 (C), 130.8 (C), 128.9 (2 x CH), 128.2 (CH), 127.2 (2 x CH), 126.2 (C), 84.6 (CH), 62.7 (CH_2), 52.2 (CH), 44.0 (CH_2), 31.4 (CH_2), 29.0 (CH_2), 26.9 (CH_2), 26.1 (CH_2), 22.4 (CH_2), 14.0 (CH_3).

Distinguishable **210e** peaks: ^1H NMR (500 MHz, $CDCl_3$) δ 6.00 (1H, d, *J* = 4.9 Hz, C**H**NO_2), 4.39 (1H, d, *J* = 4.9 Hz, C**H**Ph); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 155.0 (C), 134.6 (C), 129.2 (C), 128.39 (2 x CH), 128.37 (2 x CH), 126.5 (C), 83.8 (CH), 62.7 (CH_2), 50.1 (CH), 44.1 (CH_2), 29.2 (CH_2), 26.9 (CH_2), 26.1 (CH_2), 22.4 (CH_2).



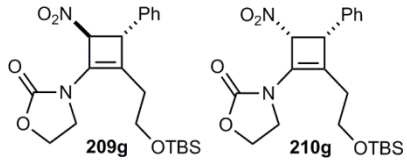
3-(4-Nitro-2-phenethyl-3-phenylcyclobut-1-enyl)oxazolidin-2-one (209f/210f)

General Procedure G was followed using ynamide **83c** (65 mg, 0.30 mmol) and purification by column chromatography (0.5% EtOAc/CH_2Cl_2 and then 20→30% EtOAc/hexane) gave an 87:13 inseparable mixture of **209f** and **210f** as a cream solid (65 mg, 59%). R_f = 0.52 (3% EtOAc/CH_2Cl_2); m.p. 98-102 ºC; IR (solid) 3063, 3026, 2922, 1755 (C=O), 1709, 1552, 1412, 1238, 1109, 759 cm^{-1}; HRMS (ESI) Exact mass calcd for $C_{21}H_{20}N_2O_4Na$ $[M+Na]^+$: 387.1315, found: 387.1319.

Data for **209f**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.41-7.29 (5H, m, Ar**H**), 7.26-7.17 (5H, m, Ar**H**), 5.49-5.47 (1H, m, C**H**NO_2), 4.33 (1H, dt, *J* = 9.1, 6.5 Hz, C$\mathbf{H}_2$O), 4.27 (1H, dt, *J* = 9.0, 7.0 Hz, C$\mathbf{H}_2$O), 3.91 (1H, s, C**H**Ph), 3.68 (1H, dt, *J* = 9.1, 7.0 Hz, C$\mathbf{H}_2$N), 3.21 (1H, dt, *J* = 9.0, 6.5 Hz, C$\mathbf{H}_2$N), 2.74-2.68 (2H, m, C$\mathbf{H}_2$C$\mathbf{H}_2$Ph), 2.54 (1H, td, *J* = 14.9, 7.5 Hz, C$\mathbf{H}_2$C$\mathbf{H}_2$Ph), 2.40-2.33 (1H, m, C$\mathbf{H}_2$C$\mathbf{H}_2$Ph); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 154.9 (C), 140.4 (C), 136.9 (C), 128.9 (2 x CH), 128.8

(C), 128.7 (2 x CH), 128.5 (2 x CH), 128.42 (C), 128.2 (CH), 127.20 (2 x CH), 126.40 (CH), 84.4 (CH), 62.7 (CH_2), 52.2 (CH), 43.3 (CH_2), 33.2 (CH_2), 28.2 (CH_2).

Distinguishable **210f** peaks: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13-7.10 (2H, m, Ar**H**), 5.99 (1H, d, *J* = 5.0 Hz, C**H**NO_2), 4.42-4.37 (1H, m, C**H**$_2$O), 3.84 (1H, ddd, *J* = 9.3, 8.9, 6.4 Hz, C**H**$_2$N), 3.48 (1H, ddd, *J* = 9.2, 8.6, 7.0 Hz, C**H**$_2$N), 2.80-2.74 (1H, m, C**H**$_2$C**H**$_2$Ph); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 154.8 (C), 140.5 (C), 134.4 (C), 128.45 (2 x CH), 128.3 (2 x CH), 127.4 (CH), 127.15 (C), 126.43 (CH), 83.7 (CH), 62.6 (CH_2), 50.0 (CH), 43.4 (CH_2), 33.0 (CH_2), 28.0 (CH_2).



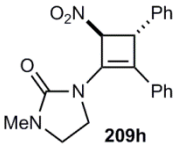
3-{2-[2-(*tert*-Butyl-dimethylsilyloxy)-ethyl]-4-nitro-3-phenylcyclobut-1-enyl}oxazolidin-2-one (209g/210g)

A slight modification of General Procedure G was followed, by conducting the reaction at 40 ºC for 6 h, using ynamide **83b** (81 mg, 0.30 mmol). Purification by column chromatography (15→25% EtOAc/hexane) gave an 84:16 inseparable mixture of **209g** and **210g** as an orange solid (79 mg, 63%). R_f = 0.53 (50% EtOAc/hexane); m.p. 112-117 ºC; IR (film) 3028, 2953, 2928, 2856, 1761 (C=O), 1707, 1550, 1411, 1250, 1097 cm^{-1}; HRMS (ESI) Exact mass calcd for $C_{21}H_{31}N_2O_5Si$ $[M+H]^+$: 419.1997, found: 419.1993.

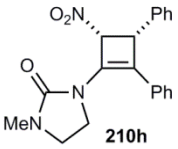
Data for **209g**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.28 (3H, m, Ar**H**), 7.26-7.22 (2H, m, Ar**H**), 5.51-5.49 (1H, m, C**H**NO_2), 4.52-4.47 (2H, m, NCH_2C**H**$_2$O), 4.12-4.07 (2H, m, C**H**$_2$N), 3.92 (1H, s, C**H**Ph), 3.62-3.53 (2H, m, C**H**$_2$OSi), 2.57-2.50 (1H, m, =CC**H**$_2$), 2.30-2.23 (1H, m, =CC**H**$_2$), 0.88 (9H, s, C(C**H**$_3$)$_3$), 0.03 (3H, s, SiC**H**$_3$), 0.02 (3H, s, SiC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 155.0 (C), 137.2 (C), 128.9 (2 x CH), 128.2 (CH), 128.1 (C), 127.2 (2 x CH), 127.1 (C), 84.5 (CH), 62.8 (CH_2), 60.1 (CH_2), 52.7 (CH), 43.9 (CH_2), 29.8 (CH_2), 25.81 (3 x CH_3), 18.21 (C), –5.5 (CH_3), –5.6 (CH_3).

Distinguishable **210g** peaks: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.03 (1H, dd, *J* = 4.9, 0.4 Hz, C**H**NO_2), 4.41 (1H, d, *J* = 4.9 Hz, C**H**Ph), 4.18 (1H, dt, *J* = 9.1, 7.1 Hz, C**H**$_2$O) 4.08-4.03 (1H, m, C**H**$_2$O), 3.69-3.64 (1H, m, C**H**$_2$N), 2.62 (1H, ddd, *J* = 14.4, 8.5, 5.5 Hz, =CC**H**$_2$), 2.40 (1H, td, *J* = 14.7, 4.9 Hz, =CC**H**$_2$), 0.87 (9H, s, C(C**H**$_3$)$_3$), 0.01 (3H, s, SiC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 154.9 (C), 134.5 (C), 128.5 (CH),

128.4 (CH), 125.5 (C), 83.9 (CH), 62.7 (CH_2), 59.9 (CH_2), 50.5 (CH), 43.8 (CH_2), 29.6 (CH_2), 25.76 (3 x CH_3), 18.17 (C).



209h



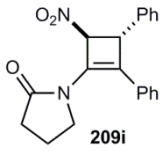
210h

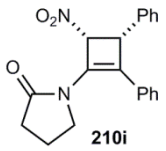
1-Methyl-3-(4-nitro-2,3-diphenylcyclobut-1-enyl)imidazolidin-2-one (209h/210h)

A slight modification of General Procedure G was followed, by conducting the reaction at 40 ºC for 6 h, using ynamide **83m** (61 mg, 0.30 mmol). Purification by column chromatography (20→40% EtOAc/hexane) gave **209h** as a yellow oil (57 mg, 55%) followed by **210h** as a yellow solid (8 mg, 8%).

Data for **209h**: R_f = 0.32 (50% EtOAc/hexane); IR (solid) 3061, 3032, 2887, 1712 (C=O), 1678, 1545, 1495, 1433, 1398, 1269 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34-7.30 (2H, m, Ar**H**), 7.30-7.24 (4H, m, Ar**H**), 7.24-7.21 (4H, m, Ar**H**), 5.68 (1H, d, *J* = 1.3 Hz, C**H**NO_2), 4.37 (1H, d, *J* = 1.3 Hz, C**H**Ph), 4.05-3.96 (1H, m, C**H**$_2$C**H**$_2$), 3.57-3.50 (3H, m, C**H**$_2$C**H**$_2$), 2.86 (3H, s, NC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 157.3 (C), 137.8 (C), 131.6 (C), 128.7 (2 x CH), 128.4 (2 x CH), 128.2 (C), 127.9 (CH), 127.84 (CH), 127.77 (2 x CH), 127.4 (2 x CH), 123.2 (C), 85.5 (CH), 52.0 (CH), 45.0 (CH_2), 42.2 (CH_2), 30.7 (CH_3); HRMS (ASAP) Exact mass calcd for $C_{20}H_{20}N_3O_3$ $[M+H]^+$: 350.1499, found: 350.1498.

Data for **210h**: R_f = 0.25 (50% EtOAc/hexane); m.p. 124-130 ºC; IR (film) 3059, 3020, 2887, 1714 (C=O), 1672, 1549, 1495, 1435, 1402, 1288 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34-7.23 (10H, m, Ar**H**), 6.23 (1H, d, *J* = 5.2 Hz, C**H**NO_2), 4.75 (1H, d, *J* = 5.2 Hz, C**H**Ph), 3.90 (1H, dt, *J* = 9.5, 5.5 Hz, C**H**$_2$C**H**$_2$), 3.82 (1H, dt, *J* = 9.4, 7.3 Hz, C**H**$_2$C**H**$_2$), 3.58 (1H, dt, *J* = 9.3, 5.5 Hz, C**H**$_2$C**H**$_2$), 3.55-3.48 (1H, m, C**H**$_2$C**H**$_2$), 2.86 (3H, s, NC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 157.4 (C), 135.2 (C), 132.2 (C), 128.9 (C), 128.6 (2 x CH), 128.5 (2 x CH), 128.3 (2 x CH), 128.2 (CH), 127.8 (CH), 127.7 (2 x CH), 122.2 (C), 84.1 (CH), 50.7 (CH), 45.0 (CH_2), 42.6 (CH_2), 30.7 (CH_3); HRMS (ESI) Exact mass calcd for $C_{20}H_{19}N_3O_3Na$ $[M+Na]^+$: 372.1319, found: 372.1321.



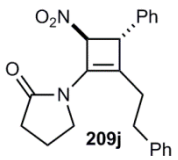


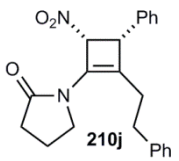
1-(4-Nitro-2,3-diphenylcyclobut-1-enyl)pyrrolidin-2-one (209i/210i)

A slight modification of General Procedure G was followed, by conducting the reaction at 40 ºC for 6 h, using ynamide **83f** (56 mg, 0.30 mmol). Purification by column chromatography (15→30% EtOAc/hexane) gave **209i** as an amorphous yellow foam (62 mg, 62%) followed by **210i** as a brown solid (16 mg, 16%).

Data for **209i**: R_f = 0.44 (50% EtOAc/hexane); IR (film) 3062, 3018, 2895, 1707 (C=O), 1674, 1548, 1394, 1257, 1215, 748 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.22 (10H, m, Ar**H**), 5.72 (1H, d, *J* = 1.3 Hz, C**H**NO_2), 4.43 (1H, d, *J* = 1.3 Hz, C**H**Ph), 3.99-3.92 (1H, m, C$\mathbf{H}_2$N), 3.51 (1H, ddd, *J* = 10.0, 7.9, 6.2 Hz, C$\mathbf{H}_2$N), 2.52-2.47 (2H, m, C$\mathbf{H}_2$C=O), 2.25-2.15 (2H, m, C$\mathbf{H}_2$$CH_2$N); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 175.5 (C), 137.2 (C), 131.0 (C), 128.8 (2 x CH), 128.7 (C), 128.6 (CH), 128.5 (2 x CH), 128.1 (2 x CH), 128.0 (CH), 127.4 (2 x CH), 126.9 (C), 85.5 (CH), 52.1 (CH), 47.4 (CH_2), 30.5 (CH_2), 19.1 (CH_2); HRMS (ASAP) Exact mass calcd for $C_{20}H_{19}N_2O_3$ $[M+H]^+$: 335.1390, found: 335.1383.

Data for **210i**: R_f = 0.35 (50% EtOAc/hexane); m.p. 64-66 ºC; IR (solid) 3062, 2957, 2924, 1707 (C=O), 1666, 1547, 1492, 1390, 1255, 734, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.22 (10H, m, Ar**H**), 6.23 (1H, d, *J* = 5.2 Hz, C**H**NO_2), 4.77 (1H, d, *J* = 5.2 Hz, C**H**Ph), 3.89 (1H, ddd, *J* = 9.9, 8.1, 5.4 Hz, C$\mathbf{H}_2$N), 3.78 (1H, ddd, *J* = 9.9, 8.0, 6.7 Hz, C$\mathbf{H}_2$N), 2.55-2.48 (2H, m, C$\mathbf{H}_2$C=O), 2.30-2.12 (2H, m, C$\mathbf{H}_2$$CH_2$N); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 175.3 (C), 134.8 (C), 131.6 (C), 128.61 (CH), 128.55 (2 x CH), 128.50 (2 x CH), 128.42 (2 x CH), 128.40 (CH), 128.1 (2 x CH), 128.0 (C), 127.5 (C), 84.1 (CH), 51.1 (CH), 47.8 (CH_2), 30.6 (CH_2), 19.1 (CH_2); HRMS (ASAP) Exact mass calcd for $C_{20}H_{19}N_2O_3$ $[M+H]^+$: 335.1390, found: 335.1384.





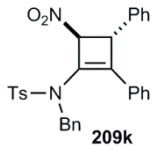
1-(4-Nitro-2-phenethyl-3-phenylcyclobut-1-enyl)pyrrolidin-2-one (209j/210j)

A slight modification of General Procedure G was followed, by conducting the reaction at 40 ºC for 6 h, using ynamide **83e** (64 mg, 0.30 mmol). Purification by column chromatography

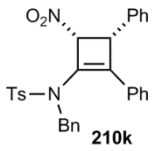
(1% EtOAc/CH_2Cl_2) gave a 90:10 inseparable mixture of **209j** and **210j** as an orange solid (45 mg, 41%). R_f = 0.27 (2% EtOAc/CH_2Cl_2); m.p. 88-92 ºC; IR (film) 3057, 3032, 2924, 1693 (C=O), 1602, 1550, 1400, 1257, 754, 700 cm^{-1}; HRMS (ESI) Exact mass calcd for $C_{22}H_{23}N_2O_3$ $[M+H]^+$: 363.1703, found: 363.1707.

Data for **209j**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.39-7.34 (2H, m, Ar**H**), 7.34-7.28 (3H, m, Ar**H**), 7.25-7.15 (5H, m, Ar**H**), 5.55-5.53 (1H, m, C**H**NO_2), 3.89 (1H, s C**H**Ph), 3.56 (1H, ddd, *J* = 9.4, 8.1, 6.7 Hz, C**H**$_2$N), 3.24 (1H, ddd, *J* = 9.4, 8.2, 5.8 Hz, C**H**$_2$N), 2.70 (2H, t, *J* = 7.2 Hz, C**H**$_2$), 2.66-2.58 (1H, m, C**H**$_2$), 2.40-2.30 (3H, m, 2 x C**H**$_2$), 2.08-1.99 (2H, m, C**H**$_2$$CH_2$N); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 174.4 (C), 140.50 (C), 137.2 (C), 129.0 (C), 128.9 (2 x CH), 128.6 (2 x CH), 128.5 (2 x CH), 128.4 (C), 128.1 (CH), 127.3 (2 x CH), 126.4 (CH), 85.1 (CH), 52.8 (CH), 46.3 (CH_2), 33.5 (CH_2), 30.2 (CH_2), 28.5 (CH_2), 18.38 (CH_2).

Distinguishable **210j** peaks: ^1H NMR (500 MHz, $CDCl_3$) δ 6.06 (1H, d, *J* = 5.0 Hz, C**H**NO_2), 4.35 (1H, d, *J* = 5.0 Hz, C**H**Ph), 3.69 (1H, dt, *J* = 8.9, 5.4 Hz, C**H**$_2$N), 3.43 (1H, dt, *J* = 9.0, 6.1 Hz, C**H**$_2$N); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 174.2 (C), 140.53 (C), 134.8 (C), 84.4 (CH), 50.7 (CH), 46.4 (CH_2), 33.2 (CH_2), 30.19 (CH_2), 28.4 (CH_2), 18.36 (CH_2).



209k



210k

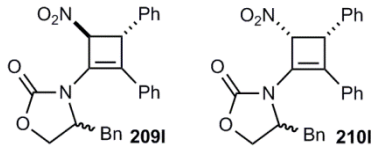
***N*-Benzyl-4-methyl-*N*-(4-nitro-2,3-diphenyl-cyclobut-1-enyl)-benzenesulfonamide (209k/210k)**

A slight modification of General Procedure G was followed, by conducting the reaction at 40 ºC for 24 h, using ynamide **83o** (108 mg, 0.30 mmol). Purification by column chromatography (5→20% EtOAc/hexane, then 0.5% EtOAc/CH_2Cl_2) gave a 95:5 inseparable mixture of **209k** and **210k** as yellow oil (21 mg, 14%). R_f = 0.48 (30% EtOAc/hexane); IR (film) 3064, 3032, 2980, 1551, 1454, 1359, 1265, 1167, 737, 698 cm^{-1}; HRMS (ES) Exact mass calcd for $C_{30}H_{26}N_2O_4S$ $[M]^+$: 510.16078, found: 510.16098.

Data for **209k**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.84 (2H, d, *J* = 8.3 Hz, Ar**H**), 7.40 (2H, d, *J* = 8.1 Hz, Ar**H**), 7.30-7.16 (9H, m, Ar**H**), 7.14-7.10 (2H, m, Ar**H**), 6.97-6.94 (2H, m, Ar**H**), 6.87 (2H, dd, *J* = 7.6, 1.8 Hz, Ar**H**), 5.18 (1H, d, *J* = 1.2 Hz, C**H**NO_2), 4.76 (1H, d, *J* = 14.2 Hz, C**H**$_2$Ph), 4.47 (1H, d, *J* = 14.2 Hz, C**H**$_2$Ph), 4.35 (1H, d, *J* = 1.0 Hz, C**H**Ph), 2.49 (3H, s, C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ

144.6 (C), 144.4 (C), 136.8 (C), 135.8 (C), 134.9 (C), 130.2 (C), 130.1 (2 x CH), 129.8 (CH), 128.9 (2 x CH), 128.6 (2 x CH), 128.5 (2 x CH), 128.3 (2 x CH), 128.2 (2 x CH), 128.1 (CH), 128.0 (CH), 127.5 (2 x CH), 127.3 (2 x CH), 126.7 (C), 89.0 (CH), 51.6 (CH_2), 49.0 (CH), 21.6 (CH_3).

Distinguishable data for **210k**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (2H, d, *J* = 8.4 Hz, Ar**H**), 5.80 (1H, d, *J* = 5.2 Hz, C**H**NO_2), 4.81 (1H, d, *J* = 14.4 Hz, C**H**$_2$Ph), 4.58 (1H, d, *J* = 14.4 Hz, C**H**$_2$Ph), 2.48 (3H, s, CH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 144.9 (C), 144.5 (C), 86.2 (CH), 51.6 (CH_2), 21.6 (CH_3).



(R)-4-Benzyl-3-(4-nitro-2,3-diphenyl-cyclobut-1-enyl)-oxazolidin-2-one (209l/210l)

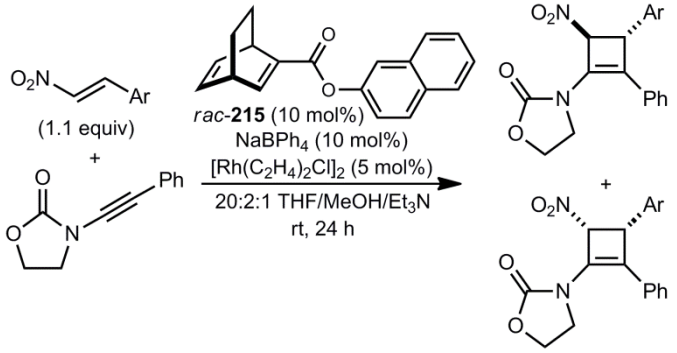
A slight modification of General Procedure G was followed, by conducting the reaction at 40 ºC for 24 h, using ynamide **83n** (83.2 mg, 0.30 mmol). The residue was purified by column chromatography (10%-15% EtOAc/hexane and then 0.5% EtOAc/CH_2Cl_2) to give **209l** as a foamy yellow solid (37 mg, 29%) (7:1 diastereomeric mixture) and **210l** as a foamy cream solid (35 mg, 27%) (8:1 diastereomeric mixture).

Data for **209l** (major diastereomer): R_f = 0.68 (50% EtOAc/hexane); IR (solid) 3061, 3028, 2926, 2853, 1761 (C=O), 1684, 1549, 1404, 1220, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43-7.34 (8H, m, Ar**H**), 7.29 (2H, dt, *J* = 6.8, 1.8 Hz, Ar**H**), 7.25-7.21 (3H, m, Ar**H**), 6.79 (2H, dd, *J* = 6.6, 2.8 Hz, Ar**H**), 5.58 (1H, d, *J* = 1.1 Hz, C**H**NO_2), 4.43-4.37 (1H, m, C**H**O), 4.37 (1H, d, *J* = 1.0 Hz, C**H**Ph), 4.33 (1H, t, *J* = 8.3 Hz, C**H**O), 4.24 (1H, dd, *J* = 8.9, 4.2 Hz, C**H**N), 3.13 (1H, dd, *J* = 13.2, 3.2 Hz, C**H**Ph), 2.63 (1H, dd, *J* = 13.2, 10.5 Hz, C**H**Ph); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 155.0 (C), 137.0 (C), 136.7 (C), 134.5 (C), 131.3 (C), 129.7 (CH), 129.2 (2 x CH), 129.1 (2 x CH), 128.9 (2 x CH), 128.7 (2 x CH), 128.5 (CH), 128.3 (2 x CH), 127.4 (2 x CH), 127.3 (CH), 124.6 (C), 87.3 (CH), 67.3 (CH_2), 57.1 (CH), 52.7 (CH), 38.2 (CH_2); HRMS (ASP) Exact mass calcd for $C_{26}H_{23}N_2O_4$ $[M+H]^+$: 427.1652, found: 427.1646.

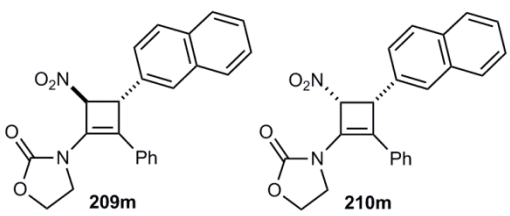
Data for **210l** (major diastereomer): R_f = 0.62 (50% EtOAc/hexane); IR (solid) 3064, 3028, 2920, 2854, 1759 (C=O), 1674, 1545, 1402, 1223, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43-7.33 (8H, m, Ar**H**), 7.31-7.27 (2H, m, Ar**H**), 7.26-7.22 (3H, m,

Ar**H**), 6.81-6.77 (2H, m, Ar**H**), 6.12 (1H, d, *J* = 5.2 Hz, C**H**NO_2), 4.72 (1H, d, *J* = 5.2 Hz, C**H**Ph), 4.58 (1H, tdd, *J* = 10.7, 8.2, 4.1 Hz, C**H**O), 4.38 (1H, t, *J* = 8.5 Hz, C**H**O), 4.28 (1H, dd, *J* = 9.1, 4.3 Hz, C**H**N), 3.35 (1H, dd, *J* = 13.4, 3.8 Hz, C**H**Ph), 2.86 (1H, dd, *J* = 13.4, 10.7 Hz, C**H**Ph); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 155.0 (C), 135.1 (C), 134.8 (C), 131.6 (C), 129.3 (CH), 129.2 (2 x CH), 129.0 (2 x CH), 128.8 (2 x CH), 128.7 (2 x CH), 128.6 (2 x CH), 128.3 (2 x CH), 127.9 (C), 127.3 (CH), 125.5 (C), 82.8 (CH), 67.3 (CH_2), 56.3 (CH), 52.0 (CH), 37.6 (CH_2); HRMS (ASP) Exact mass calcd for $C_{26}H_{23}N_2O_4$ $[M+H]^+$: 427.1652, found: 427.1647.

Rh-Catalyzed [2+2] Cycloaddition of Ynamide 83a with Nitroalkenes 172b-e: General Procedure H



A solution of $[Rh(C_2H_4)_2Cl]_2$ (5.8 mg, 0.015 mmol), *rac*-**215** (8.3 mg, 0.03 mmol), and $NaBPh_4$ (10.3 mg, 0.03 mmol) in THF (0.5 mL) was stirred at room temperature for 15 min. A solution of the ynamide **83a** (56 mg, 0.30 mmol) and the appropriate nitroalkene (0.33 mmol) in THF (2.5 mL) and MeOH (0.3 mL) was then added *via* cannula. Et_3N (150 μL) was added and the mixture was stirred at room temperature for 24 h, filtered through a short plug of silica gel using EtOAc (40 mL) as eluent, and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography gave the cyclobutenamides.



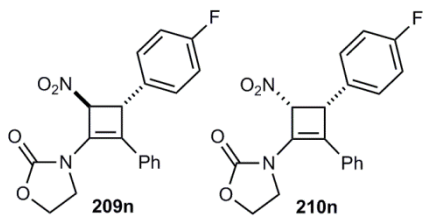
3-(3-Naphthalen-2-yl-4-nitro-2-phenylcyclobut-1-enyl)oxazolidin-2-one (209m/210m)

A slight modification of General Procedure H was followed, by conducting the reaction at 40 ºC for 6 h, using nitroalkene **172b** (66 mg, 0.33 mmol).

Purification by column chromatography (15→30% EtOAc/hexane) gave **209m** as an amorphous yellow foam (54 mg, 47%) followed by **210m** as a yellow solid (12 mg, 10%).

Data for **209m**: R_f = 0.39 (50% EtOAc/hexane); IR (solid) 3057, 3022, 2922, 1755 (C=O), 1681, 1545, 1404, 1224, 775, 754 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.11 (1H, d, *J* = 8.4 Hz, Ar**H**), 7.90 (1H, d, *J* = 7.7 Hz, Ar**H**), 7.78 (1H, d, *J* = 8.3 Hz, Ar**H**), 7.61 (1H, ddd, *J* = 8.4, 6.9, 1.4 Hz, Ar**H**), 7.56 (1H, ddd, *J* = 8.0, 7.0, 1.1 Hz, Ar**H**), 7.40-7.31 (5H, m, Ar**H**), 7.31-7.27 (1H, m, Ar**H**), 7.18 (1H, d, *J* = 6.5 Hz, Ar**H**), 5.67 (1H, d, *J* = 1.4 Hz, C**H**NO_2), 5.27 (1H, s, C**H**Ar)**,** 4.61-4.52 (2H, m, C$\mathbf{H}_2$O), 4.26 (1H, dt, *J* = 9.0, 6.0 Hz, C$\mathbf{H}_2$N), 3.78 (1H, tt, *J* = 15.8, 8.0 Hz, C$\mathbf{H}_2$N); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 155.7 (C), 133.9 (C), 132.8 (C), 131.7 (C), 130.7 (C), 129.5 (C), 129.0 (CH), 128.9 (CH), 128.8 (2 x CH), 128.7 (CH), 128.0 (2 x CH), 126.9 (CH), 126.2 (CH), 125.7 (C), 125.3 (CH), 125.2 (CH), 122.7 (CH), 85.6 (CH), 63.3 (CH_2), 47.0 (CH), 44.7 (CH_2); HRMS (ESI) Exact mass calcd for $C_{23}H_{18}N_2O_4Na$ $[M+Na]^+$: 409.1159, found: 409.1158.

Data for **210m**: R_f = 0.32 (50% EtOAc/hexane); m.p. 104-107 ºC; IR (solid) 3057, 3012, 2922, 1751 (C=O), 1682, 1551, 1409, 1230, 1124, 781 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.22 (1H, d, *J* = 8.5 Hz, Ar**H**), 7.87 (1H, d, *J* = 8.1 Hz, Ar**H**), 7.79 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.62 (1H, ddd, *J* =8.4, 6.9, 1.3 Hz, Ar**H**), 7.55-7.51 (1H, m, Ar**H**), 7.38-7.30 (7H, m, Ar**H**), 6.43 (1H, d, *J* = 5.1 Hz, C**H**NO_2), 5.62 (1H, d, *J* = 5.1 Hz, C**H**Ar), 4.62-4.56 (2H, m, C$\mathbf{H}_2$O), 4.11 (2H, t, *J* = 7.9 Hz, C$\mathbf{H}_2$N); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 155.6 (C), 133.7 (C), 132.1 (C), 131.0 (C), 129.7 (C), 129.1 (CH), 128.94 (CH), 128.92 (CH), 128.7 (2 x CH), 128.5 (C), 128.1 (2 x CH), 126.52 (CH), 126.46 (CH), 126.0 (C), 125.9 (CH), 125.0 (CH), 122.8 (CH), 83.9 (CH), 63.1 (CH_2), 46.3 (CH), 45.2 (CH_2); HRMS (ESI) Exact mass calcd for $C_{23}H_{22}N_3O_4$ $[M+NH_4]^+$: 404.1605, found: 404.1607.



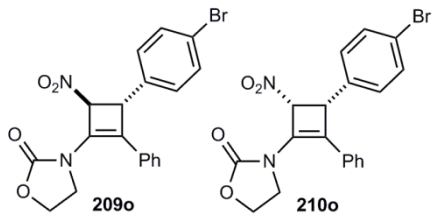
3-[3-(4-Fluorophenyl)-4-nitro-2-phenylcyclobut-1-enyl]oxazolidin-2-one (209n/210n)

General Procedure H was followed using nitroalkene **172c** (55 mg, 0.33 mmol) and

purification by column chromatography (20→30% EtOAc/hexane) gave **209n** as a yellow solid (71 mg, 67%) followed by **210n** as a yellow oil (18 mg, 17%).

Data for **209n**: R_f = 0.44 (50% EtOAc/hexane); m.p. 143-146 ºC; IR (solid) 3055, 2959, 2920, 1753 (C=O), 1678, 1547, 1510, 1404, 1223, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41-7.32 (3H, m, Ar**H**), 7.26-7.19 (4H, m, Ar**H**), 7.02-6.97 (2H, m, Ar**H**), 5.61 (1H, d, *J* = 1.1 Hz, C**H**NO_2), 4.58-4.52 (2H, m, C$\mathbf{H}_2$O), 4.40 (1H, d, *J* = 1.1 Hz, C**H**Ar), 4.18 (1H, dt, *J* = 8.9, 6.2 Hz, C$\mathbf{H}_2$N), 3.78-3.70 (1H, m, C$\mathbf{H}_2$N); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 162.5 (C, d, *J* = 247.1 Hz), 155.7 (C), 132.6 (C, d, *J* = 3.2 Hz), 130.3 (C), 129.3 (C), 129.1 (2 x CH, d, *J* = 8.5 Hz), 129.0 (CH), 128.8 (2 x CH), 128.0 (2 x CH), 125.6 (C), 115.9 (2 x CH, d, *J* = 21.7 Hz), 85.0 (CH, d, *J* = 1.2 Hz), 63.3 (CH_2), 50.8 (CH), 44.6 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –113.7 (1F, tt, *J* = 8.6, 5.3 Hz, Ar**F**); HRMS (ESI) Exact mass calcd for $C_{19}H_{15}N_2O_4FNa$ $[M+Na]^+$: 377.0908, found: 377.0911.

Data for **210n**: R_f = 0.33 (50% EtOAc/hexane); IR (film) 3020, 2922, 2850, 1759 (C=O), 1678, 1556, 1508, 1406, 1215, 750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40-7.32 (3H, m, Ar**H**), 7.29-7.23 (4H, m, Ar**H**), 7.01-6.96 (2H, m, Ar**H**), 6.16 (1H, d, *J* = 5.2 Hz, C**H**NO_2), 4.76 (1H, d, *J* = 5.2 Hz, C**H**Ar), 4.63-4.50 (2H, m, C$\mathbf{H}_2$O), 4.11-3.99 (2H, m, C$\mathbf{H}_2$N); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 162.8 (C, d, *J* = 247.6 Hz), 155.5 (C), 130.8 (C), 130.2 (2 x CH, d, *J* = 8.3 Hz), 130.1 (C, d, *J* = 3.1 Hz), 129.0 (CH), 128.8 (2 x CH), 128.2 (C), 127.9 (2 x CH), 126.2 (C), 115.6 (2 x CH, d, *J* = 21.7 Hz), 83.7 (CH, d, *J* = 0.8 Hz), 63.1 (CH_2), 49.6 (CH), 45.0 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –113.3 (1F, tt, *J* = 8.6, 5.3 Hz, Ar**F**); HRMS (ESI) Exact mass calcd for $C_{19}H_{14}N_2O_4F$ $[M-H]^-$: 353.0943, found: 353.0935.

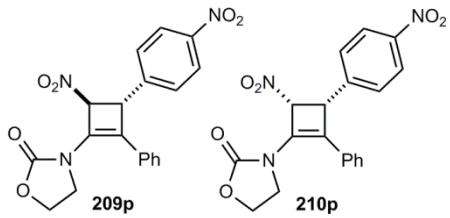


3-[3-(4-Bromophenyl)-4-nitro-2-phenylcyclobut-1-enyl]oxazolidin-2-one (209o/210o)

General Procedure H was followed using nitroalkene **172d** (75 mg, 0.33 mmol) and purification by column chromatography (15→30% EtOAc/hexane) gave **209o** as an amorphous yellow foam (82 mg, 66%) followed by **210o** as a pale yellow solid (22 mg, 18%).

Data for **209o**: R_f = 0.47 (50% EtOAc/hexane); IR (solid) 3062, 3026, 2922, 1755 (C=O), 1682, 1547, 1487, 1402, 1225, 1011 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45-7.41 (2H, m, Ar**H**), 7.40-7.32 (3H, m, Ar**H**), 7.25-7.21 (2H, m, Ar**H**), 7.14-7.10 (2H, m, Ar**H**), 5.61 (1H, d, *J* = 1.3 Hz, C**H**NO_2), 4.59-4.50 (2H, m, C**H**$_2$O), 4.37 (1H, d, *J* = 0.7 Hz, C**H**Ar), 4.18 (1H, dt, *J* = 8.9, 6.2 Hz, C**H**$_2$N), 3.74 (1H, dd, *J* = 16.8, 9.0 Hz, C**H**$_2$N); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 155.7 (C), 135.8 (C), 132.1 (2 x CH), 130.2 (C), 129.1 (2 x CH), 129.1 (CH), 128.9 (C), 128.8 (2 x CH), 127.9 (2 x CH), 125.7 (C), 122.2 (C), 84.6 (CH), 63.3 (CH_2), 50.9 (CH), 44.6 (CH_2); HRMS (ESI) Exact mass calcd for $C_{19}H_{19}N_3O_4{}^{79}Br$ $[M+NH_4]^+$: 432.0553, found: 432.0556.

Data for **210o**: R_f = 0.36 (50% EtOAc/hexane); m.p. 128-132 ºC; IR (solid) 3059, 2957, 2924, 1755 (C=O), 1676, 1547, 1477, 1402, 1228, 1205 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44-7.40 (2H, m, Ar**H**), 7.38-7.33 (3H, m, Ar**H**), 7.25-7.22 (2H, m, Ar**H**), 7.18-7.14 (2H, m, Ar**H**), 6.17 (1H, d, *J* = 5.2 Hz, C**H**NO_2), 4.73 (1H, d, *J* = 5.2 Hz, C**H**Ar), 4.58 (1H, dt, *J* = 9.1, 6.2 Hz, C**H**O), 4.53 (1H, dt, *J* = 8.9, 7.7 Hz, C**H**O), 4.10-3.99 (2H, m, C**H**$_2$N); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 155.5 (C), 133.5 (C), 131.7 (2 x CH), 130.7 (C), 130.2 (2 x CH), 129.0 (CH), 128.8 (2 x CH), 127.9 (2 x CH), 127.8 (C), 126.3 (C), 122.8 (C), 83.5 (CH), 63.1 (CH_2), 49.7 (CH), 45.0 (CH_2); HRMS (ASAP) Exact mass calcd for $C_{19}H_{16}N_2O_4{}^{79}Br$ $[M+H]^+$: 415.0288, found: 415.0279.



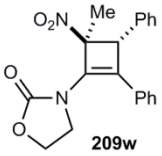
3-[4-Nitro-3-(4-nitrophenyl)-2-phenylcyclobut-1-enyl]oxazolidin-2-one (209p/210p)

General Procedure H was followed using nitroalkene **172e** (64 mg, 0.33 mmol) and purifcation by column chromatography (25→35% EtOAc/hexane then 1% EtOAc/CH_2Cl_2) gave a mixture of **209p** and **210p** that could not be completely separated (81:19 ratio, respectively) as a cream foam (77 mg, 67%). IR (solid) 3082, 3026, 2922, 1755 (C=O), 1682, 1548, 1518, 1404, 1346, 1227 cm^{-1}; HRMS (ESI) Exact mass calcd for $C_{19}H_{15}N_3O_6Na$ $[M+Na]^+$: 404.0853, found: 404.0859.

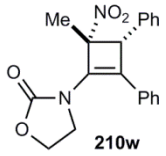
Data for **209p**: R_f = 0.32 (50% EtOAc/hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 8.19-8.15 (2H, m, Ar**H**), 7.45-7.41 (2H, m, Ar**H**), 7.41-7.33 (3H, m, Ar**H**), 7.26-7.22 (2H,

m, Ar**H**), 5.65 (1H, d, *J* = 1.4 Hz, C**H**NO_2), 4.64-4.53 (2H, m, C$\mathbf{H}_2$O), 4.52 (1H, d, *J* = 1.2 Hz, C**H**Ar), 4.21 (1H, dt, *J* = 8.9, 6.2 Hz, C$\mathbf{H}_2$N), 3.76 (1H, dt, *J* = 9.0, 7.7 Hz, C$\mathbf{H}_2$N); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 155.6 (C), 147.8 (C), 144.2 (C), 129.8 (C), 129.4 (CH), 129.0 (2 x CH), 128.5 (2 x CH), 127.9 (C), 127.8 (2 x CH), 126.0 (C), 124.2 (2 x CH), 84.0 (CH), 63.4 (CH_2), 50.6 (CH), 44.6 (CH_2).

Distinguishable **210p** data: R_f = 0.21 (50% EtOAc/hexane): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16-8.12 (2H, m, Ar**H**), 7.48-7.45 (2H, m, Ar**H**), 6.24 (1H, d, *J* = 5.2 Hz, C**H**NO_2), 4.88 (1H, d, *J* = 5.2 Hz, C**H**Ar), 4.12-4.03 (2H, m, C$\mathbf{H}_2$N); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 155.4 (C), 148.0 (C), 142.0 (C), 130.4 (C), 129.6 (2 x CH), 129.3 (CH), 128.9 (2 x CH), 127.7 (2 x CH), 123.7 (2 x CH), 83.5 (CH), 63.2 (CH_2), 49.5 (CH), 45.0 (CH_2).



209w



210w

3-[4-methyl-4-nitro-2,3-diphenylcyclobut-1-enyl]oxazolidin-2-one (209w/210w)

A slight modification of General Procedure H was followed, by conducting the reaction at 40 ºC for 24 h, using nitroalkene **172l** (53.8 mg, 0.33 mmol). Purification by column chromatography (18→30% EtOAc/hexane) gave **209w** as an amorphous white foam (17 mg, 18%) followed by **210w** as a yellow oil (16 mg, 17%).

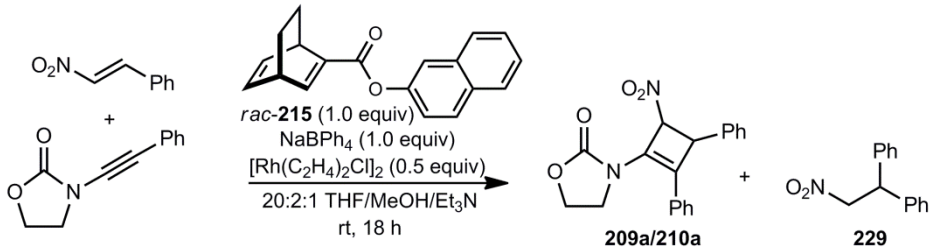
Data for **209w**: R_f = 0.55 (50% EtOAc/hexane); IR (solid) 3057, 3030, 2922, 1759 (C=O), 1676, 1537, 1404, 1215, 1109, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.32 (3H, m, Ar**H**), 7.32-7.28 (5H, m, Ar**H**), 7.16-7.12 (2H, m, Ar**H**), 4.57-4.49 (2H, m, C$\mathbf{H}_2$O), 4.52 (1H, s, C**H**Ph), 4.14 (1H, dt, *J* = 8.6, 6.4 Hz, C**H**N), 3.81-3.74 (1H, m, C**H**N), 1.60 (3H, s, C$\mathbf{H}_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 155.3 (C), 134.8 (C), 130.9 (C), 130.8 (C), 129.7 (C), 129.2 (2 x CH), 128.9 (CH), 128.63 (2 x CH), 128.60 (2 x CH), 128.13 (2 x CH), 128.11 (CH), 91.3 (C), 63.2 (CH_2), 55.1 (CH), 45.1 (CH_2), 18.8 (CH_3); HRMS (ES) Exact mass calcd for $C_{20}H_{18}N_2O_4$ $[M]^+$: 350.12611, found: 350.12614.

Data for **210w**: R_f = 0.44 (50% EtOAc/hexane); IR (film) 3057, 3028, 2924, 1759 (C=O), 1676, 1541, 1406, 1221, 1115, 734 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.31 (3H, m, Ar**H**), 7.30-7.26 (5H, m, Ar**H**), 7.23-7.19 (2H, m, Ar**H**), 4.60-4.49 (2H, m, C$\mathbf{H}_2$O), 4.38 (1H, s, C**H**Ph), 4.06 (1H, app. q, *J* = 8.5 Hz, C**H**N), 3.96 (1H, dt, *J* =

9.0, 6.1 Hz, C**H**N), 2.23 (3H, s, C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 154.8 (C), 134.6 (C), 131.1 (C), 129.3 (2 x C), 128.8 (CH), 128.51 (2 x CH), 128.50 (2 x CH), 128.42 (CH), 128.36 (2 x CH), 128.2 (2 x CH), 93.4 (C), 63.1 (CH_2), 57.7 (CH), 45.2 (CH_2), 21.7 (CH_3).

Arylation of Nitroalkene

1-Nitro-2,2-diphenylethane (229)



A solution of $[Rh(C_2H_4)_2Cl]_2$ (19.4 mg, 0.05 mmol), *rac*-**215** (27.4 mg, 0.10 mmol), and $NaBPh_4$ (34.2 mg, 0.10 mmol) in THF (1.0 mL) was stirred at room temperature for 15 min. A solution of ynamide **83a** (18.7 mg, 0.10 mmol) and nitroalkene **172a** (14.9 mg, 0.10 mmol) in THF (2.0 mL) and MeOH (0.3 mL) was then added *via* cannula. Et_3N (150 μL) was added and the mixture was stirred at room temperature for 18 h, filtered through a short plug of silica gel using EtOAc (40 mL) as eluent, and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography (3→35% EtOAc/hexane) gave product **229** (7 mg, 31%) as a colourless oil, followed by cyclobutenamides **209a** and **210a** as a 81:19 diastereomeric mixture (22 mg, 65%).

Data for **229**: R_f = 0.30 (10% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.32 (4H, m, Ar**H**), 7.30-7.23 (6H, m, Ar**H**), 5.02-4.98 (2H, m, C**H**$_2$NO$_2$), 4.92 (1H, dd, *J* = 9.1, 7.1 Hz, C**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 139.2 (2 x C), 129.0 (4 x CH), 127.64 (4 x CH), 127.58 (2 x CH), 79.2 (CH), 48.9 (CH_2). Spectral data was in agreement with literature data.[131]

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7. Appendix

List of Publications

1.[*] **Rhodium-Catalyzed Carbometalation of Ynamides with Organoboron Reagents** Gourdet, B.; Smith D. L.; Lam, H. W. *Tetrahedron*, **2010**, *66*, 6026-6031.

2.[†] **Palladium-Catalyzed Hydroacyloxylation of Ynamides** Smith, D. L.; Goundry, W. R. F.; Lam, H. W. *Chem. Comm.*, **2012**, *48*, 1505-1507.

3.[‡] **Rhodium-Catalyzed [2+2] Cycloaddition of Ynamides with Nitroalkenes** Smith, D. L.; Reddy Chidipudi, S.; Goundry, W. R.; Lam, H. W. *Org. Lett.*, **2012**, *14*, 4934-4837.

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